The role of rehabilitation in improving short and long term outcomes for survivors of critical illness

D J McWilliams

PhD 2018

The role of rehabilitation in improving short and long term outcomes for survivors of critical illness

David Joseph McWilliams

A thesis submitted in partial fulfilment of the requirements of the Manchester Metropolitan University for the degree of Doctor of Philosophy by Published Work (Route 2)

Department of Health Professions

Faculty of Health, Psychology and Social Care

Manchester Metropolitan University

2018

Abstract

This thesis aims to evaluate the role of rehabilitation in improving outcomes for patients admitted to critical care. Patients admitted to critical care experience significant muscle weakness, which when present is associated with prolonged stays in both ICU and hospital and higher mortality levels. Although overall survival rates from critical illness are improving, survivors are often left with significant and ongoing physical, functional and psychological dysfunction. Preventing the physical consequences of critical illness and supporting recovery from intensive care therefore remains a high priority area for critical care practice and research.

This thesis presents and critiques 11 peer reviewed publications and 2 national guidelines to demonstrate the role of rehabilitation in improving outcomes. The first 5 papers presented investigate the impact of a novel post ICU rehabilitation programme to improve long term outcomes. This begins with the initial feasibility testing of the programme and demonstrates development of the analysis into a more robust multi-centre trial. The impact of exercise based rehabilitation is evaluated with regards to physical, psychological and quality of life measures.

The next 6 papers presented investigate the potential for early rehabilitation which commences in ICU to reduce the negative impact of critical illness and improve patient outcomes. Specifically they evaluate the impact of a structured approach to rehabilitation within critical care, identifying the key components required and potential barriers to implementation. The findings of the papers included in this thesis provide valuable insights to inform future research opportunities and challenges in order to continue to develop the evidence for critical illness rehabilitation and recovery.

Acknowledgements

I have been fortunate to receive funding for my doctoral fees and study leave from Queen Elizabeth hospital in Birmingham. I would like to thank my academic advisors, Professor James Selfe and Dr Suzanne Gough for their support, feedback, encouragement, and guidance throughout the process. I have also been fortunate to have a number of positive mentors over the past 10 years and would like to acknowledge the support and guidance of Dr Catherine Snelson, Dr Jane Eddleston and Catherine Elliott.

Finally, I want to thank my wife Emma and my daughters Natasha and Elsie for their patience, encouragement, and for keeping me positive throughout.

Abbreviations and glossary

6MWT	Six minute walk test
ACPRC	Association of chartered physiotherapists in respiratory care
ARDS	Acute respiratory distress syndrome
AT	Anaerobic threshold
CG	Clinical guideline
CPET	Cardiopulmonary exercise testing
CSP	Chartered society of physiotherapy
DoH	Department of health
ECMO	Extracorporeal membrane oxygenation
ESICM	European society of intensive care medicine
HADS	Hospital anxiety and depression score
ICU	Intensive care unit
LOS	Length of stay
MDT	Multidisciplinary team
MMS	Manchester mobility score
NHS	National health service
NICE	National Institute for Health and Care Excellence
NIHR	National institute for health research
PEPSE	Programme of enhanced physiotherapy and exercise
PF	Physical function
PPI	Patient and public involvement
QIP	Quality improvement project
QOL	Quality of life
QS	Quality standard
RCT	Randomised controlled trial
REMAIC	Recovery of muscle after intensive care

RFPB	Research for patient benefit
SOFA	Sequential organ failure assessment
SF36	Short form 36 health survey
UK	United Kingdom
US	United States
VO2	Oxygen consumption

CONTENTS

List of figures

List of tables

Chapter 1 – Introduction

This thesis provides a novel exploration of the role of rehabilitation in improving short and long term outcomes for survivors of critical illness. In this chapter, I discuss the drivers behind this thesis including the negative impact of critical illness and ongoing physical and psychological sequelae observed in survivors. The chapter also presents my backstory, including my development as a researcher, followed by an overview of the structure of this thesis and research questions addressed by the articles included.

1.1 Drivers behind this thesis

Mortality rates for patients treated in intensive care units (ICU) have decreased over the past two decades (28% vs 31%, $p<0.001$), particularly for those with severe sepsis (18.4% vs 35%, $P<0.01$), creating an increase in the number of ICU survivors (Esteban et al., 2013; Kaukonen et al., 2014). Despite the positive improvement in survival rates, survivors of critical illness often experience significant physical, psychological and cognitive morbidity; a process now termed 'Post Intensive Care Syndrome'. Post intensive care syndrome describes a range of new or worsening disorders commonly seen in survivors of critical illness as a direct consequence of the ICU stay, independent from the underlying pathology (Needham et al., 2012). These effects can last months to years after hospital discharge (Herridge et al., 2011), with a negative impact on employment and income in ICU survivors and their care-givers; whilst mortality and utilisation of primary care services are elevated and remain high in the immediate post-discharge period (Griffiths et al., 2013). When considering successful outcomes

from critical illness, it is now acknowledged that it is no longer sufficient or appropriate to consider survival alone (Desai et al., 2011) and an increased focus has been placed on the role of rehabilitation to improve both short and long term outcomes.

1.2 Backstory and development as a researcher

I developed a specific interest in respiratory physiotherapy early in my career following two undergraduate student placements within the National extracorporeal membrane oxygenation (ECMO) centre at Glenfield Hospital in Leicester. I was inspired at the time by the knowledge and skills of my clinical educator, who was a well-respected and dynamic member of the critical care team, as well as the acute nature working with critically ill patients. I graduated in 2002 with a First Class Honours in Physiotherapy and subsequently completed my core rotations at Blackpool Victoria Hospital. In 2003 I made the decision to specialise within respiratory care, competing rotations in cardiothoracics, acute medicine, pulmonary rehabilitation, specialist surgery and critical care. I was then appointed to a static post within critical care and specialist surgery at Manchester Royal Infirmary in 2005. At the time I was struck by two contemporary issues common in practice across the critical care units where I had worked:

1. Despite the often significant level of physical debilitation and need for high intensity of rehabilitation in the ward environment, no specific follow up rehabilitation was provided following hospital discharge, other than standard community based services even for those who were most debilitated.

2. The lack of rehabilitation occurring for patients within the intensive care unit. This was still apparent once patients were awake and in the recovery phase of their illness, with rehabilitation often starting only once they had been transferred to the ward.

The 13 papers included in this thesis (see Table 1.1) highlight my work to further investigate and attempt to address these two related issues. Full copies of each included paper are provided in Appendix 2.

Table 1.1 – Papers included, methodology used and declaration of contribution

Number	Publication	Methodology	Percentage contribution
1	**McWilliams, D.J.**, Atkinson, J.F.D., Conway, D.H. (2009) 'The impact and feasibility of a physiotherapy led, exercise based rehabilitation programme for intensive care survivors.' *Physiotherapy Theory and Practice.* 25(8):566-71	Prospective cohort feasibility study	80%
2	Benington, S., **McWilliams, D.,** Eddleston, J., Atkinson, D. (2012) 'Exercise testing in survivors of intensive care--is there a role for cardiopulmonary exercise testing?' *Journal of Critical Care,* 27(1) pp. 89-94.	Prospective cohort feasibility study	50%
3	**McWilliams, D.,** Benington, S., Atkinson, D. (2016) 'Outpatient based physical rehabilitation for survivors of prolonged critical illness: A randomised controlled trial.' *Physiotherapy Theory and Practice*, 32(3) pp. 179-190	Randomised controlled trial	50%
4	Jones, C., Eddleston, J., McCairn, A., Dowling, S., **McWilliams, D.,** Coughlan, E., Griffiths, R.D. (2015) 'Improving rehabilitation following critical illness through outpatient physiotherapy classes and essential amino acid supplement: a randomised, controlled trial.' *Journal of critical care,* 30(5) pp. 901-7.	Randomised controlled trial (2x2 factorial design)	40%
5	Major, M.E., Kwakman, R., Kho, M., Connolly, B., **McWilliams, D.,** Denehy, L., Hanekom, S., Patman, S., Gosselink, R., Jones, C., Nollet, F., Needham, D.M., Engelbert, R.H., van der Schaaf, M. (2016) 'Surviving critical illness: what is next? An expert consensus statement on physical rehabilitation after hospital discharge.' *Critical Care*. 20(1):354 [online] [Accessed on 20th September 2017] DOI: 10.1186/s13054-016-1508-x	Delphi Consensus	5%
6	**McWilliams, D.,** Weblin, J., Atkins, G., Bion, J., Williams, J., Elliott, C., Whitehouse, T., Snelson, C. (2015) 'Enhancing rehabilitation of mechanically ventilated patients in the intensive care unit: a quality improvement project.' *Journal of Critical Care*, 30(1) pp.13-8.	Prospective before and after controlled study	90%
7	Bakhru, R.N., Wiebe, D.J., **McWilliams, D.J.,** Spuhler, V.J., Schweickert, W.D. (2015) 'An Environmental Scan for Early Mobilization Practices in United States Intensive Care Units.' *Critical Care Medicine*, 43(11) pp. 2360-2369.	Telephone survey (stratified randomised sampling)	25%

8	Bakhru, R., **McWilliams, D.J.,** Wiebe, D.J., Spuhler, V.J., Schweickert, W.D. (2016) 'Intensive Care Unit Structure Variation and Implications for Early Mobilization Practices: An International Survey.' *Annals of the American Thoracic Society,* 13(9):pp. 1527-37.	Telephone survey (stratified randomised sampling)	25%
9	**McWilliams, D.,** Atkins, G., Hodson, J., Snelson, C. (2017) 'The Sara Combilizer as an early mobilisation aid for critically ill patients: A prospective before and after study.' *Australian Critical Care*. 30(4) pp. 189-195.	Prospective before and after controlled study	90%
10	Snelson, C., Jones, C., Atkins, G., Hodson, J., Whitehouse, T., Veenith, T., Thickett, D., Reeves, E., McLaughlin, A., Cooper, L., **McWilliams, D.** (2017) 'A comparison of earlier and enhanced rehabilitation of mechanically ventilated patients in critical care compared to standard care (REHAB): study protocol for a single-site randomised controlled feasibility trial.' *Pilot and Feasibility Studies*, 17(3):19 [online] [Accessed 20th September 2017] DOI: 10.1186/s40814-017-0131-1.	Randomised controlled feasibility trial protocol	80%
11	**McWilliams, D.,** Jones, C., Atkins, G., Hodson, J., Whitehouse, T., Veenith, T., Reeves, E., Cooper, L., Snelson, C. (2018) Earlier and enhanced rehabilitation of mechanically ventilated patients in critical care: A feasibility randomised controlled trial. *Journal of critical care. Apr (44). pp. 407-412*	Randomised controlled feasibility trial (stratified randomisation)	80%
12	National Institute for Health and Care Excellence [NICE]. (2009) *Rehabilitation after critical illness.* London: NICE (Nice guideline no 83)	N/A	5%
13	National Institute for Health and Care Excellence [NICE]. (2017) *Rehabilitation after critical illness*. London: NICE (Nice quality standard no 158)	N/A	5%

To address the issue regarding the lack of rehabilitation within critical care units I decided to collect data regarding current mobilisation levels and limiting factors which were present. At the time of my appointment in 2005, there were no validated scales of mobility for critically ill patients so I developed a novel tool called the Manchester mobility score (MMS) as a way of quantifying current

mobility levels. This small internal project identified a number of potentially reversible barriers to early mobilisation of patients within critical care, helping me to develop a more robust structure for rehabilitation delivery. For example, barriers existed regarding staffing levels and prioritisation which could potentially have been reduced through the introduction of better timetabling of physiotherapy sessions and collaborative working with other members of the multidisciplinary team. The results of this work were published in the association of chartered physiotherapists in respiratory care (ACPRC) journal (McWilliams et al., 2008). Ongoing data collection using the MMS demonstrated its usefulness as a tool to capture key rehabilitation process measures, including time taken to first mobilise and the highest level of mobility achieved within critical care. This tool has now been validated (McWilliams et al., 2016) and is used in critical care units both nationally and internationally, where it is currently being translated into Portuguese for use in Brazil.

At around the same time, in order to address the issue of ongoing rehabilitation for patients following hospital discharge, I set up a specific outpatient based, post ICU rehabilitation programme which to my knowledge was the first such programme in the world for this patient population. The results for the first cohort of patients to complete the programme were submitted as an abstract to the European Society of Intensive Care Medicine (ESICM) congress in 2007, allowing me to present my findings in poster format in Barcelona. For this work I was also given an award for best young researcher of 2007 at a research event hosted by central Manchester foundation trust. I was subsequently invited to present further details regarding the programme at an early mobilisation network meeting in May 2008 in Toronto,

Canada chaired by Professor Dale Needham, and invited to join the group as a physiotherapy representative for the United Kingdom. Within this position I have regularly lectured on the topic of rehabilitation within and after critical care including multiple presentations in Europe (>30), North America (10) and Asia (4).

In recognition of my developing expertise in the area of critical illness rehabilitation I was invited to a NICE stakeholder meeting as part of the development process for NICE CG50 - Care of the Acutely unwell adult (NICE 2007). Although NICE CG50 (2007) was originally planned to incorporate recommendations regarding rehabilitation, it was decided at the stakeholder meeting due to the size of the topic it would be more appropriate to produce an additional guideline on this topic. I was invited to apply and was successful in gaining a place on the guideline development group for NICE CG83 (2009) – Rehabilitation after critical illness. As my expertise in critical care physiotherapy and rehabilitation continued to develop, I developed a growing reputation in this area both nationally and internationally. This led to my appointment as the critical care champion for the ACPRC, where I served a 6-year term from 2007 – 2013.

I was appointed to the post of Clinical Specialist Physiotherapist for critical care in 2010, initially at Manchester Royal Infirmary before moving to a similar post at the Queen Elizabeth hospital in Birmingham in 2012. By this point I was now being invited as a regular speaker at the European Society of Intensive Care Medicine (ESICM) annual congress as one of the only physiotherapists to be part of the main programme. My rising International profile led to my appointment in 2015 as a member of the nurse and allied health professionals committee for the ESICM

and the chair for the physiotherapy working group sub-committee. In this role I have worked to increase physiotherapy and allied health professional involvement in conferences and study events in what was previously a very medically focussed organisation. As a result of this work 2017 saw a record number of physiotherapy related abstracts (n=45) submitted to the annual congress in Vienna and physiotherapy involvement embedded in a number of key platform sessions.

In 2016 I was appointed to a Consultant Physiotherapy post, becoming one of only 10 respiratory physiotherapy consultants in the UK. It was in this post I developed close links with the National Institute for Health Research, Surgical Reconstruction and Microbiology Research Centre at the Queen Elizabeth Hospital in Birmingham leading to a number of publications (McWilliams et al., 2015; McWilliams et al., 2017; Snelson et al., 2017). More recently I was once again successful in becoming a guideline development group member for the development of a quality standard for rehabilitation after critical illness (NICE, 2017), as well as recently being appointed as an expert advisor for the National Institute for Health and Care excellence. In addition to the specific papers which form this submission a list of additional articles and book contributions are included to illustrate a more complete picture of my contribution to the evidence base (Appendix 2).

The research publications included in this thesis demonstrate my development into an expert clinician, with research as a key component throughout in the evaluation and development of my practice. My research journey has paralleled the Complex Interventions Framework (Craig et al., 2008), the key elements of which are shown in Figure 1.1. This journey started with small internal feasibility projects before

developing larger, more complex and methodologically robust evaluations in the form of randomised controlled trials and multicentre projects, with future work streams aimed at evaluating the implementation of my research findings. A summary of research methodologies used are provided in Table 1.1. My early research projects took the form of small, internally funded service evaluations or were supported by small charity grants. As my career and profile have increased I have been able to access large scale grants from industrial partners totalling over £100,000 (McWilliams et al., 2017) and was a co applicant in an NIHR research for patient benefit grant totalling £227,526 (Jones et al., 2015). I have won awards for best young researcher within my local critical care network (2007) and twice won the best abstract award at the ESICM annual congress (2013 and 2017). I have had the opportunity to work with collaborators both on a National and International scale including respected experts such as Professor Dale Needham from the John Hopkins Hospital, Baltimore (Major et al., 2016), Dr William Schweickert from University of Pennsylvania School of Medicine in Philadelphia (Bakhru et al., 2015; Bakhru et al., 2016) and Professor Richard Griffiths from Whiston hospital and the Institute of aging and chronic disease at the University of Liverpool (Jones et al., 2015).

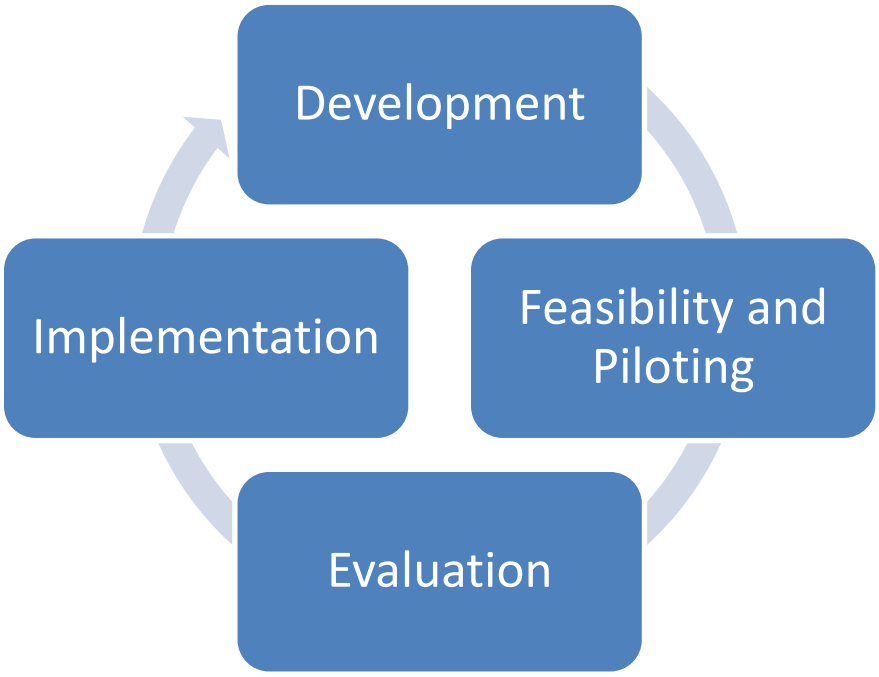

Figure 1.1 Key elements of the development and evaluation process according to the complex interventions framework (Adapted from Craig et al., 2008)

The 11 papers and 2 clinical guidelines included in this thesis and shown in Table 1.1 and represent my work in two main focal areas,

1. Post ICU rehabilitation (following hospital discharge).
2. Early rehabilitation (within critical care)

The relationship between these two areas and the papers included are represented in Figure 1.3, with the 2 clinical guidelines spanning rehabilitation within critical care and in the community following hospital discharge.

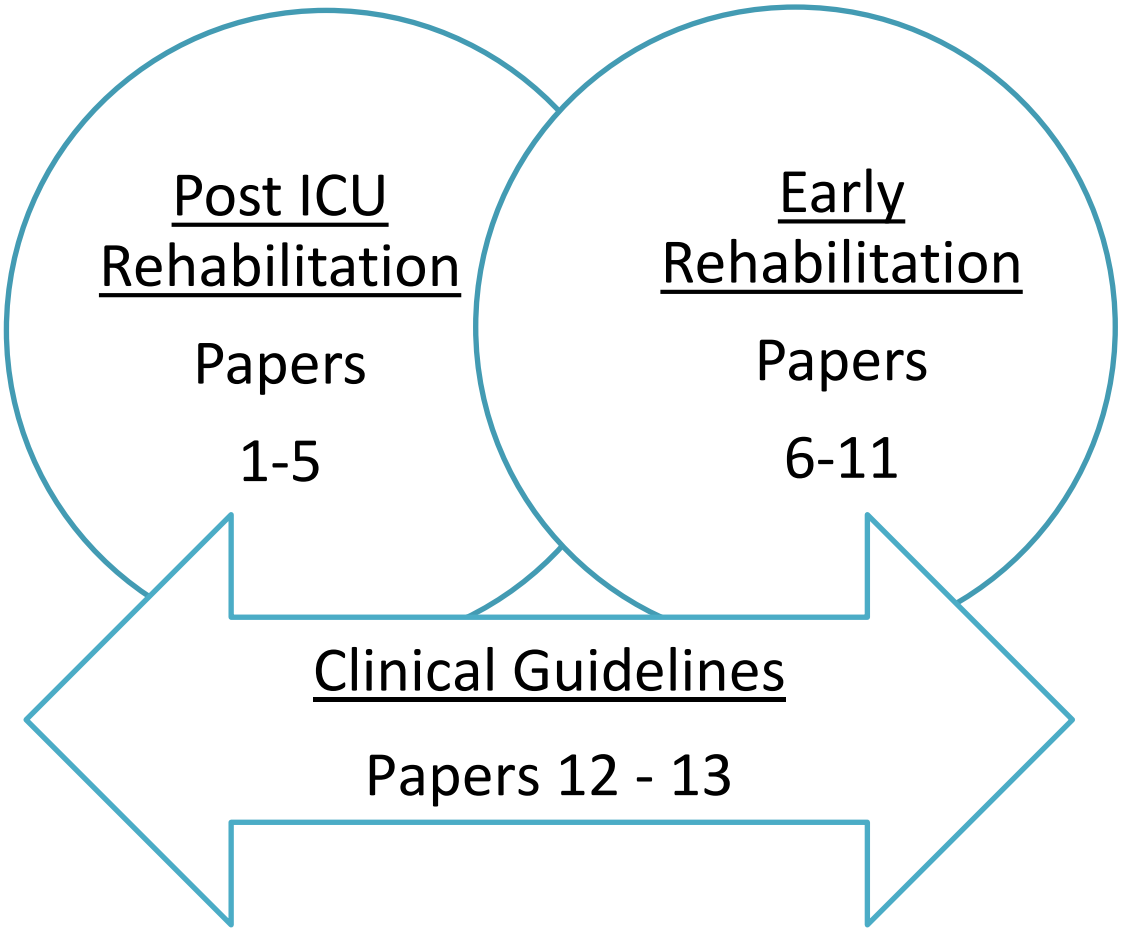

Figure 1.2 Summary of papers to be included

1.3 Structure of thesis

My thesis begins in chapter 2 by exploring the literature analysing the impact of critical illness on short and long term outcomes. This narrative literature review will discuss the potential role for rehabilitation for patients admitted to critical care and throughout their recovery. Chapter 2 concludes with a summary of the current research gaps and outlines my research questions. Specifically, this thesis aims to develop and evaluate the role of rehabilitation in improving outcomes for survivors of critical illness.

Also included throughout this thesis are two national guidelines produced by the National Institute for Health and Care Excellence (NICE, 2009; NICE, 2017). The original NICE guideline 'CG83 (NICE, 2009)– Rehabilitation after critical illness' for which this doctoral candidate was an author, emphasised the need for structured rehabilitation for patients admitted to critical care and a need for more research in this area. This guideline offered best practice advice on the care of adults with rehabilitation needs as a result of a period of critical illness from the point of admission and extending into the community setting. The interventions provided in the included publications are based on this advice and associated recommendations.

Chapter 3 explores the concept of post ICU rehabilitation and includes five of my publications in this area. This chapter discusses the reduced physical function and corresponding poor long term outcomes seen in survivors of critical illness.
Five publications are included which include the evaluation of the feasibility and impact of an outpatient based rehabilitation programme as a potential method to improve overall recovery, reduce the need for ongoing care and facilitate a return to normal activity and employment.

Chapter 4 discusses the rationale for earlier and structured rehabilitation, hypothesising that earlier treatment may help to minimise the physical decline experienced by patients admitted to critical care with the potential to improve recovery both in the short and longer term. Six publications are included in this chapter, which evaluated the feasibility and impact of one such programme and aimed to identify specific barriers to implementation. The chapter concludes with

lessons learned from my previous studies and the resultant protocol and results for a feasibility randomised controlled trial.

Chapter 5 concludes this thesis, providing an overview of the strengths and limitations and novel aspects from my publications. Overall learning points from this thesis are then discussed with regards to future research opportunities and challenges in order to continue to develop the evidence base for critical illness rehabilitation and recovery.

Chapter 2 - Background

This chapter begins by exploring the impact of a period of critical illness and the corresponding admission to critical care. This will include a summary of physical and non-physical morbidity experienced in both the short and long term. For the purpose of this thesis, short term will relate to outcomes experienced from admission up and to hospital discharge, whilst long term will consider those in the post hospital discharge period. To aid the reader in gaining perspective on the development of my research publications, the state of the evidence for rehabilitation between 2000 and 2010 will be presented.

2.1 Impact of critical illness

Patients admitted to ICU often experience significant weakness, with muscle mass decreasing at a rate of 2–4% per day during the first 2–3 weeks of ICU admission (Brower et al., 2009). The causes of this high rate of muscle loss are multifactorial, including factors such as sarcopenia from premorbid conditions, sepsis and prolonged immobility, with those staying in the ICU for >10 days and those aged >50 years most at risk (Jones and Griffiths, 2000). In the short term, the development of muscular weakness within the ICU is associated with prolonged periods of mechanical ventilation, with increases in the duration of weaning of up to 7 times ($p<0.001$) for those with severe weakness (Hermans et al., 2008). ICU acquired weakness has also been demonstrated to be directly associated with prolonged ICU and hospital length of stay and increased in-hospital mortality (Garnacho-Montero et al., 2005). As a result, survivors of critical illness are often

left with severe functional impairments and reduced pace and degree of recovery (Griffiths and Hall, 2010).

In the longer term, numerous follow-up studies have demonstrated significant and long lasting physical, psychological and socioeconomic problems in survivors of critical illness, all of which contribute to a reduced health-related quality of life (QOL) (Iwashyna et al., 2010). A landmark paper published in 2003 highlighted the significant physical and psychological morbidity experienced by survivors of critical illness (Herridge et al., 2003). This study by Herridge and colleagues followed a cohort of acute respiratory distress syndrome (ARDS) survivors for one year, with assessments taking place at 3, 6 and 12 months. Physical function, assessed using the six minute walk test (6MWT), was only 49% of predicted levels at 3 months following hospital discharge when compared to aged matched healthy adults. Less than half of patients had returned to work at 1 year, with reported reasons for non-return being persistent weakness, fatigue and poor functional status.

Extended stays on the ICU are recognised to have psychological implications for patients (Jones and Griffiths, 2000), with high levels of depression and anxiety still present up to 2 years following discharge from hospital (Hopkins et al., 2005). Long-stay patients also report a severely decreased quality of life, with a systematic review identifying statistically significant ($p<0.05$) and clinically meaningful (> 5 points) decrements in all domains of the 36 item short form health survey (SF36) in comparison to aged matched healthy participants at 12 months following hospital discharge (Dowdy et al., 2005). This reduced function has a

negative impact on employment and income, with mortality and utilisation of primary care services high in the immediate post discharge period (Cheung et al., 2006). Preventing the physical consequences of critical illness and supporting recovery from intensive care therefore remains a high priority area for critical care practice and research (Griffiths and Jones, 2007).

2.2 State of the evidence (2000 – 2010)

Due to the significant ongoing physical and nonphysical morbidity experienced by survivors of critical illness, national guidelines for critical care services recommended the provision of patient centred rehabilitation services which should continue following hospital discharge (DoH, 2005; NICE, 2009). Despite this, critical care follow up services remained rare. A survey of 298 critical care services within the UK found only 30% of hospitals offered any form of follow up, with the majority of these in a nurse led clinic format (Griffiths et al., 2006). Only 51% had access to other services, with less than 10% of those surveyed having access to any form of physiotherapy for patients following hospital discharge. No studies had evaluated the potential impact of exercise based rehabilitation programmes to improve outcomes.

Also during this period, as well as considering how to improve the recovery of critical care survivors, an increased focus was being placed on the potential to prevent or minimise the impact of a period of critical illness. There was growing evidence to demonstrate the safety and feasibility of early mobilisation during

critical illness (Bailey et al., 2007; Thomsen et al., 2008). When introduced programmes of early mobilisation, defined as rehabilitation and mobilisation activities that begin immediately after stabilisation of physiologic derangements and before liberation from mechanical ventilation, were associated with improvement in a number of short term outcomes. These include a reduction in both ICU and hospital length of stay, as well as improved functional ability at the point of hospital discharge (Morris et al., 2008; Needham et al., 2010). In the study by Morris and colleagues (2008), control patients took on average 6 days longer to mobilise out of bed for the first time compared to those receiving daily physiotherapy, with the result being significantly longer stays in both ICU (5.5 vs. 6.9 days, $p=0.025$) and on the wards (11.2 vs. 14.5 days, $p=0.006$). This was also a similar finding to a study by Needham et al (2010), where a significantly increased median number of physiotherapy treatments (7 vs 1, $p<0.001$) was associated with reductions in both ICU and hospital length of stay ($P<0.05$). Early and structured rehabilitation has also been associated with reduced incidence of delirium (Schweickert et al., 2009), improvements to respiratory parameters such as peak inspiration and peak expiration, and improved peripheral muscle strength in comparison with patients who receive no physiotherapy (Chiang et al., 2006).

By 2010, although there was a growing evidence base in North American populations, there was a paucity of European-based research into the impact of early rehabilitation programs within critical care, particularly when applied to mechanically ventilated patients. The delivery of physiotherapy within critical care in the United States (US) is very different from that in Europe, with US-based studies suggesting that only 13% of patients received physiotherapy within the ICU

(Morris et al., 2008), with treatment provided usually limited to a median of 1 session per patient (Needham et al., 2010). This differs from that provided within Europe and Australia where daily physiotherapy is already an established standard of care (Parker et al., 2013). It is therefore unclear whether improvements seen in the United States are applicable to European-based models of health care delivery and processes of physiotherapy practice, or whether it was the similar introduction of daily physiotherapy and the focus on rehabilitation which was having a positive impact. Consequently there is little evidence supporting how best to deliver rehabilitation in those units with already established physiotherapy services.

With the increased focus on long term outcomes and rehabilitation needs of critical care survivors, in 2009 the National Institute for Health and Care Excellence (NICE) produced a specific clinical guideline entitled, 'Critical Illness Rehabilitation' (NICE, 2009). The authors (which include this Doctoral candidate) produced a guideline which advocated the need for a seamless rehabilitation pathway, specifically one which commences at the point of ICU admission and continues into the post hospital discharge period. According to NICE (2006), recommendations for the care of individuals are formulated by healthcare professionals based on the best available evidence. In order to formulate recommendations, the guideline was structured around specific questions and thorough literature searches were completed regarding each of these. Selected articles were then reviewed and only the highest quality of evidence (i.e. randomised controlled trials and meta-analyses) was used to formulate specific recommendations. In the absence of an appropriate quality of evidence, expert

opinion from the group was used. At the time, only one randomised controlled trial was identified and included as part of the physical rehabilitation review (Jones et al., 2003). This study by Jones and colleagues did demonstrate a positive impact in response to a self-directed exercise programme for patients following critical care discharge, although no input was provided within critical care and overall recovery at 6 months was shown to be incomplete.

Although highlighting the important role of physiotherapy and rehabilitation, due to a lack of robust evidence in the form of meta-analyses or randomised controlled trials, the guideline was unable to provide more substance in terms of specific components of service delivery. Subsequently it did however highlight areas for much needed research. This was also highlighted as a key topic for physiotherapy research, with critical illness rehabilitation included in 4 out of the top 10 topics in the physiotherapy research priority project (CSP, 2010). This project represented a joint initiative between the Chartered Society of Physiotherapy and the James Lind Alliance where 32/43 expert panelists were asked to identify and prioritise topics for research over the following 3 years. The specific recommendations relevant to this thesis were:

- The effect of a physiotherapist-led early mobility programme in Intensive Therapy Units on patients' long term outcomes of function, mobility and quality of life
- Comparative work on the role of the physiotherapist in post-critical care rehabilitation and follow-up clinics, to look at long-term outcomes and possible predictors of functional outcome

- Investigating interventions which could enhance recovery in patients with critical illness
- Exercise interventions for patients with critical illness: feasibility and physiological and functional outcomes

2.3 Gaps in the literature and research questions

Table 2.1 summarises the gaps in the literature and maps them to the associated research questions from the included papers (references in parenthesis) and chapter locations.

Table 2.1: Literature gaps, research questions and chapter location

Research Gap	Research Question(s)	Corresponding Thesis Chapter
1. Are exercise based rehabilitation programmes an effective method to improve long term physical and non-physical outcomes for survivors of critical illness?	What is the impact of an outpatient based rehabilitation programme on exercise capacity and anxiety and depression scores in a cohort of adult intensive care survivors? (Paper 1: McWilliams et al., 2009). What is the impact of an outpatient based rehabilitation programme on exercise capacity and health related quality of life in a randomised controlled trial? (Paper 3: McWilliams et al., 2016). Does a 6-week program of enhanced physiotherapy and structured exercise and an essential amino acid supplement drink improve physical and psychological recovery? (Paper 4: Jones et al., 2015)	3
2. Which patients are most in need of ongoing rehabilitation following	Is it feasible to use cardiopulmonary exercise testing (CPET) for the early assessment of cardiorespiratory	3

hospital discharge and what are the key outcomes to measure recovery in critical care survivors?	fitness in general adult intensive care unit survivors? (Paper 2: Benington et al., 2012) What do experts recommend for physiotherapy interventions and key outcomes to measure for survivors of critical illness? (Paper 5: Major et al., 2016)	
3. Development of a robust and measurable structure for rehabilitation delivery within critical care	What is the impact of an early and enhanced rehabilitation program for mechanically ventilated patients in a large tertiary referral, mixed-population intensive care unit? (Paper 6: McWilliams et al., 2015) Does the introduction of a specialist seating device reduce the time taken to first mobilise patients who have been ventilated for at least five days and at risk of ICU acquired weakness? (Paper 9: McWilliams et al., 2017) What are the differences between a structured early rehabilitation intervention and standard care for patients admitted to critical care and what outcomes are most appropriate for inclusion in a future definite randomised controlled trial? (Paper 10: Snelson et al., 2017; Paper 11: McWilliams et al., 2018)	4
4. The identification of specific barriers to the implementation of early rehabilitation programmes and methods to overcome them	What is the current level of diffusion of early mobility practice and what are the environmental factors that may influence its practice? (Paper 7: Bakhru et al., 2015; Paper 8: Bakhru et al., 2016)	4

2.4 Chapter summary

This chapter has presented a summary of the negative and significant impact of a period of critical illness. It has discussed the current evidence base to support the need for rehabilitation, both within critical care and following hospital discharge, and identified the gaps in the current evidence base addressed by the papers included in this thesis.

Chapter 3 – Post ICU Rehabilitation studies

This chapter is based on publications 1-5 presented in Table 1.1 (p13), all of which are pertinent to the rehabilitation of critically ill patients following discharge from critical care and aims to address research gaps 1 and 2 (Table 3.1), by answering the following research questions:

Table 3.1 Research gaps and associated research questions

Research Gap	Research questions
Research gap 1. Are exercise based rehabilitation programmes an effective method to improve long term physical and non-physical outcomes for survivors of critical illness?	What is the impact of an outpatient based rehabilitation programme on exercise capacity and anxiety and depression scores in a cohort of adult intensive care survivors? (Paper 1: McWilliams et al., 2009). What is the impact of an outpatient based rehabilitation programme on exercise capacity and health related quality of life in a randomised controlled trial? (Paper 3: McWilliams et al., 2016). Does a 6-week program of enhanced physiotherapy and structured exercise and an essential amino acid supplement drink improve physical and psychological recovery? (Paper 4: Jones et al., 2015)
Research gap 2. Which patients are most in need of ongoing rehabilitation following hospital discharge and what are the key outcomes to measure recovery in critical care survivors?	Is it feasible to use cardiopulmonary exercise testing (CPET) for the early assessment of cardiorespiratory fitness in general adult intensive care unit survivors? (Paper 2: Benington et al., 2012) What do experts recommend for physiotherapy interventions and key outcomes to measure for survivors of critical illness? (Paper 5: Major et al., 2016)

3.1 Background

At the time of devising a protocol for the first paper included (McWilliams et al., 2009); only one study had explored the impact of rehabilitation for critical care survivors. Jones et al. (2003) investigated the impact of a 6-week self-help rehabilitation manual to aid recovery for patients admitted for ≥ 48 hours to one of 3 UK based ICU's. The manual consisted of 93 pages of text, diagrams and illustrations tailored to the needs of patients recovering from critical illness and included a 6 week self-directed exercise programme. Physical function scores, assessed using the Short Form 36 (SF36) health related QOL questionnaire, were significantly higher for those using the manual in comparison to controls at both 8 weeks (35 vs 46, $p<0.05$) and 6 months (39 vs 50, $p<0.05$). However, the overall level of physical function achieved at 6 months was still lower than that seen in a healthy population and appeared similar to those seen in patients with a moderate or severe illness (Jones, 2003). Therefore, although conferring some benefit over standard care the use of a self-directed manual alone still resulted in an incomplete recovery and ongoing reduced QOL.

A more recent study using the same self-help manuals in conjunction with intensive care follow-up clinics failed to demonstrate any improvement in QOL scores over and above standard care (Cuthbertson et al., 2009). In part, this may have been due to population differences, with Cuthbertson et al. (2009) including all patients admitted to critical care regardless of length of stay. As patients with longer stays in ICU are most at risk of ICU acquired weakness, the inclusion of those with shorter stays may have resulted in a population with less physical and

non-physical morbidity and hence a more complete recovery. One other potential factor is the increased awareness of the long term morbidity associated within critical illness and a subsequent improvement in standard care since the original publication by Jones et al. (2003). This created the first research gap highlighted in Table 3.1 for the potential benefit for exercise based rehabilitation programmes as a method of delivering rehabilitation and improving outcomes for survivors of critical illness.

3.2 The feasibility of exercise based rehabilitation programmes

To try to reverse the negative impact of critical illness, I set up a post ICU rehabilitation class in 2005 which was the first of its kind in the United Kingdom. My publications in this area demonstrate the development of my research through the complex intervention framework (research gap 1. Table 3.1 p32). Paper 1 represents the first analysis of this programme in the form of a feasibility trial, evaluating the impact of a structured, outpatient based rehabilitation programme for survivors of critical illness (McWilliams et al., 2009). Assessing feasibility is an important process in evaluating the acceptability, compliance, intervention delivery alongside recruitment and retention rates and suitability of chosen outcomes (Craig et al., 2008). As principal investigator, I selected to include patients who were admitted to a UK based ICU and ventilated for ≥ 48 hours for inclusion the feasibility trial, which is the same inclusion criteria used previously by Jones et al. (2003). This seemed appropriate in order to investigate my intervention using a population who had previously demonstrated an incomplete recovery. Participants completed one supervised circuit based exercise class each week for a period of 6

weeks. As no previous literature existed in this area, the novel exercise circuit I devised was based on previously published guidance for cardiac and pulmonary rehabilitation programmes. Although these programmes were not directly designed for those recovering from a period of critical illness, this seemed appropriate as patients with chronic respiratory disease or heart disease often have similar restrictions in physical function and multiple comorbidities.

Progression of exercise was defined according to pre-set criteria, specifically achievement of targets of 50-70% of heart rate reserve, calculated using the Karvonen formula (Karvonen et al., 1957), and a modified Borg breathlessness score (Borg, 1982) of 3-4 (moderate to somewhat severe). These ensured patients were exercising at the optimal level for cardiorespiratory training whilst providing high internal validity to the intervention. Participants were also advised to complete 2 further exercise sessions unsupervised at home, although no data was collected with regards to adherence with this part of the programme. Significant improvements were observed from baseline scores in walking distance on both the 6-minute walk test ($p<0.001$) and incremental shuttle walk test ($p<0.001$). Corresponding reductions were also observed in both anxiety and depression levels (assessed using the Hospital Anxiety and Depression scale) on completion of the programme.

3.2.1 Lessons learned

The supervised component of the intervention was acceptable to patients, with excellent recruitment (97%) and retention rates (88%) to the trial. Good adherence was also demonstrated with the exercise programme, with all patients completing at least five of the six supervised sessions. The lack of measurement regarding self-directed activity did however fail to assess the overall feasibility of the intervention and the use of a convenience sample may have created the potential for selection bias. Significant improvements ($p<0.001$) were seen from baseline in outcomes assessed for physical function, anxiety and depression. As no control group was available for comparison only limited conclusions could be drawn on any overall benefit to recovery compared to standard care. It was unclear whether the improvements in exercise capacity had a significant impact on a patient's daily function or quality of life.

3.3 Evolving evidence

Following publication of my feasibility trial (McWilliams et al., 2009) a small number of other studies were completed by other researchers in this area, assessing a variety of methods to improve long-term outcomes for survivors of critical illness. A Cochrane review was completed in 2015 evaluating the effectiveness of exercise based rehabilitation programmes following critical care discharge (Connolly et al., 2015). Although 6 papers were identified as part of the Cochrane review process, only 3 included specific outpatient based components and are relevant for this chapter (Jones et al., 2003; Elliott et al., 2011; Batterham et al., 2014). Due to inconsistency of study findings and wide variability in

characteristics of interventions and outcomes, the review was unable to determine the overall effect of exercise based interventions on either functional capacity or health related quality of life for survivors of critical illness. Each of the included studies were found to have important limitations which has helped to further develop our understanding of this area. The paper by Jones et al. (2003) has been discussed earlier in this chapter.

The study by Elliott et al., (2011) was a multi-centre trial including 12 hospitals in Australia (n=195) which evaluated the effect of a home-based rehabilitation programme for intensive care survivors. Patients were randomly allocated to either the 8 week rehabilitation programme or standard care and the authors chose the physical function component of the SF36 as a validated measure of assessing overall health status. To ensure compliance patients were either visited at home or received a telephone call on a weekly basis. On analysis, there were no significant differences between groups in terms of physical function or QOL at either 8 weeks or 6 months (Elliott et al., 2011). There were however potential important limitations and lessons to be learned from this study. Firstly inclusion criteria included patients admitted to ICU ≥48 hours and ventilated for at least 24 hours. Previous research has demonstrated significantly shorter periods of recovery for those with ICU lengths of stay ≤ 4 days (Daffurn, 1994) and the inclusion of these patients may have limited the overall impact. Additionally, the intervention consisted of only three supervised activity sessions (60-90 minute home visits) performed on weeks 1, 3 and 6. Although a standard approach was utilised, the programmes were individualised with no specific definition to guide intensity level and as such the specific exercise programmes utilised may have varied

significantly. The exercise components were also delivered by different healthcare professionals, either a physiotherapist, exercise physiologist or a registered nurse, with no specific training to guide the intervention increasing the likelihood of varying degrees of exercise intensity and methods of progression.

The other outpatient based study included in the Cochrane review was completed by Batterham et al., (2014) which examined the impact of an 8-week hospital-based exercise-training programme on physical fitness and quality-of-life. Fifty-nine patients aged between 18 and 65 who had been ventilated for at least 3 days were recruited to the trial from 2 large teaching hospitals in the UK. The intervention comprised of 2 sessions of physiotherapy-lead cycle ergometry for 30mins at moderate intensity and 1 equivalent unsupervised session each week for 8 weeks. Intensity of exercise was titrated according to patients perceived exertion levels during each session. Although an accelerated recovery in anaerobic threshold in the first 9 weeks was seen in comparison to controls, this was not sustained at 26 weeks. Importantly, no significant differences were observed for QOL between groups at any time point despite the apparent accelerated rate of recovery. Once again a number of limitations were present. Firstly, a large degree of missing data was seen for the primary outcome of anaerobic threshold was seen at the 9 week assessment, with data only available for 30/59 patients. This may have resulted in an under or over estimation of the results seen. As an exploratory trial the sample size was low which may have contributed to potentially important baseline differences in terms of illness severity and hospital length of stay. The selection of only patients < 65 years meant that the mean age of the sample population was relatively young (40.5 and 42.7 for

control and intervention groups respectively) compared to that of a general ICU population which has a mean of 60.9 years (ICNARC, 2018) limiting generalisability of any findings.

3.4 Evaluating the impact of post ICU rehabilitation programmes

To further investigate the impact of the outpatient based rehabilitation class from paper 1 (McWilliams et al., 2009) I designed and completed a randomised controlled trial which led to 2 further publications (Benington et al., 2012; McWilliams et al., 2016) in attempt to address research gap's 1 and 2 (Table 3.1, p32). The study was funded through the award of a Manchester Wellcome Trust Clinical Research Facility grant (£10,000) and a Central Manchester NHS Foundation Trust Research for Patient Benefit grant (£10,000). To try to gain a robust insight into the physical response to the exercise programme, cardiopulmonary exercise testing (CPET) was used as the primary outcome measure, which was perceived to represent the gold standard for exercise testing in patients with cardiac and pulmonary disease. For this project I collaborated with Dr Dougal Atkinson who had a special interest in CPET within my trust. The major advantage of CPET over other objective measures of exercise capacity (e.g., 6MWT) is that it provides information that may identify cardiac, respiratory, or musculoskeletal contributions to any exercise limitation present. At the time CPET had never been performed either nationally or internationally in survivors of critical illness in the immediate post hospital discharge period. As a novel area of research we therefore published paper 2, summarising the results seen for the first 50 patients to complete the CPET (Benington et al., 2012).

We found that in our cohort significant (P<0.01) exercise limitation was present with peak VO2 at only 56% and anaerobic threshold (AT) 41% of predicted values taken from a previously published reference population of sedentary, healthy volunteers respectively. This is a similar level of exercise limitation seen in patients with moderate to severe heart failure (Weber and Janicki, 1985). A prospectively stratified subgroup comparison showed that patients ventilated for 14 days or more had a significantly lower AT (p=0.009) and peak VO2 (p=0.23) than those ventilated for 5 to 14 days. This work supported earlier publications demonstrating the significant and ongoing physical limitations seen in survivors of critical illness (Herridge et al., 2011; Brummel, 2015), particularly those with longer periods of mechanical ventilation, and further added to the case for ongoing rehabilitation following hospital discharge.

Paper 3 represents the results of the RCT, comparing the recovery in CPET parameters between participants attending for rehabilitation and a control group (McWilliams et al., 2016). Given the positive results seen from my previous feasibility trial (McWilliams et al., 2009), a randomised controlled trial was chosen to evaluate the impact of the post ICU rehabilitation programme. This work formed the 'Evaluation' component of the complex interventions framework, with randomisation chosen to prevent selection bias (Craig et al., 2008). The exercise programme followed the same format as that previously evaluated, with once weekly supervised exercise sessions provided in a group setting and 2 unsupervised sessions completed independently at home. Sessions were well attended (with all participants completing at least 5 of the 7 supervised sessions). The primary outcome was change in CPET parameters (Anaerobic Threshold (AT)

and peak VO2), with a quality of life measure (the SF36) also included as a secondary outcome to gain further perspectives on the impact of any potential physical improvements seen. Although all participants demonstrated a significant ($p<0.05$) improvement from baseline over the trial period, no significant differences were seen between groups for either AT ($p=0.74$) or peak VO2 ($p=0,68$). Despite this lack of physical improvement, health related QOL scores were significantly higher both clinically (> 5 points) and statistically ($p<0.05$), in all domains for the patients in the intervention group.

3.4.1 Lessons learned

A number of limitations were apparent which may have limited the findings of this study. Significant baseline differences were observed between groups, with those in the intervention arm spending significantly longer in critical care (29.1 vs 22.2 days) and having been ventilated for longer (19.8 vs 12.7 days). With the findings from paper 2 (Benington et al., 2012) suggesting those with longer periods of mechanical ventilation showing the greatest physical deficit, this may have resulted in a more debilitated population in the intervention group. In hindsight the lack of stratification during randomisation may have therefore been a significant limitation.

Despite being regarded as the gold standard for exercise testing, the selection of CPET as the primary outcome may also have been a significant limitation. On further review, a number of other rehabilitation studies have failed to demonstrate

improvements in CPET despite reported improvements in function or quality of life. Interestingly in our trial, QOL scores were significantly higher in all domains for those patients who attended the rehabilitation programme. This benefit to QOL had not been observed in any previous trials of physical rehabilitation in this population but, as a secondary outcome, the study was not directly powered to detect this change. Interestingly, when comparing the SF36 scores from our trial to other previous studies it was noted that patients in our control group had similar physical function (PF) scores to those seen in previous trials at 3 months following hospital discharge (Elliott et al., 2011; Denehy et al., 2013; Batterham et al., 2014), whilst the PF scores for our intervention group were higher than all of those previously seen. This started to develop my thinking regarding what were the important outcomes to assess for survivors of critical illness, as well as what were the key components of the intervention which may be important.

3.5 Post ICU rehabilitation and nutrition

Once I had completed recruitment for the RCT outlined above (McWilliams et al., 2016) I was approached by leading experts in critical care follow up Professor Richard Griffiths and Dr Christina Jones. These experts were renowned with the development of the first ever follow up clinic for critical care survivors and have published a considerable number (>150) of papers on the impact of critical illness and long-term outcomes. I was invited to collaborate as they were keen to incorporate my novel exercise programme into their study evaluating a specific nutritional supplement to aid recovery. Jointly we developed a study entitled the recovery of muscle after intensive care (REMAIC) (Jones et al., 2015). I was a co-

applicant on a successful application for funding from the National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) grant totalling £227,526, with this study representing the first multi-centre trial I had been involved with. The addition of the extra research group members, coupled with the findings from my previous research (McWilliams et al., 2009; Benington et al., 2012; McWilliams et al., 2016) allowed further development of the intervention and methodology for evaluation.

This project aimed to evaluate the impact of an amino acid supplement in conjunction with a programme of enhanced physiotherapy and exercise (PEPSE). We chose to include patients over 45 years of age and a length of stay of >5 days from three UK based hospitals (Jones et al., 2015). Professor Griffiths' previous research had demonstrated that skeletal muscle protein synthesis is reduced following a period of immobility, particularly in older adults (Griffiths, 1996). The addition of essential amino acid supplements have been demonstrated as a potent stimuli for muscle rebuilding in healthy elderly participants (Volpi et al., 2003), particularly when used in combination with active exercise (Borsheim et al., 2008). Given the high rate of muscle loss associated with critical illness, coupled with the added impact of age related sarcopenia where adults aged 45 years may have lost 10% of their muscle prior to ICU admission, we hypothesised the combination of an amino acid supplement with structured exercise may further enhance recovery in older survivors of critical illness.

The PEPSE component of the intervention was based on the original post ICU rehabilitation programme I had developed (McWilliams et al., 2009) but I also now included the addition of 1:1 ward based sessions whilst the patient was still in hospital awaiting discharge. It was hypothesised that by starting the programme as soon as patients were physically ready rather than waiting for hospital discharge we may have been able to further enhance recovery. As well as further developing the programme I was responsible for training of physiotherapists at the other centres and ensuring effective dissemination of the PEPSE programme. This process was supported through the development of a standard operating procedure with specified metrics to guide exercise intensity and progression. This process included regular reviews with the therapy staff, providing quality assurance and ensuring adherence with the protocol for intervention delivery. A power calculation (80% power at 0.05 significance) was performed using the 6MWT results from my earlier feasibility trial (McWilliams et al., 2009). A total of 180 patients were required for the study, randomised to 45 in each arm as part of a 2x2 factorial design. A factorial design was chosen to assess each intervention independently and in combination, with the hypothesis that the combination of exercise and nutrition would demonstrate the largest effect size on recovery.

Patients were recruited to the REMAIC study (Jones et al., 2015) once they had been discharged from critical care and could walk a minimum distance of 30m. This aimed to target patients earlier in their recovery but still ensured they would be able to meet the requirements of the exercise programme. Whilst still in the acute hospital, those patients randomised to the PEPSE groups received additional physiotherapy and structured exercise sessions three times weekly,

which then continued on a weekly basis in the form of a structured rehabilitation class after hospital discharge. The administration of the amino acid supplement was double blinded, with patients consuming the supplement or a placebo twice daily for a period of 3 months. Patients receiving the PEPSE and the amino acid supplement had the biggest gains in distance walked in 6-minute walking test ($p<0.0001$). There were also significant reductions in the hospital anxiety ($p=0.036$) and depression scores ($p=0.0009$) (HADS) in both groups receiving the PEPSE programme.

3.5.1 Lessons learned

Commencing the intervention during the in-patient stay and the use of an exercise diary resulted in excellent rates of attendance and adherence to the programme. Unfortunately, as with the previously discussed RCT (McWilliams et al., 2016) the study failed to reach its recruitment target, with only 93 out of the required 180 patients consented within the trial period. The decision to include only patients over 45 years of age and a minimum walking distance of 30m proved to be a significant limitation, with 22% (n=164) of eligible patients unable to reach the minimum walking distance for inclusion whilst in hospital. Whilst highlighting the significant physical limitation present in survivors of critical illness, paradoxically the exclusion of these patients may have failed to include a population most in need of ongoing rehabilitation. In the future trials it would be beneficial to include a lower intensity level of the programme to include these patients or include a process to recruit them once their mobility had improved sufficiently.

3.6 Delphi consensus

Paper 5 represents the culmination of my developing expertise in the area of physical rehabilitation for survivors of critical illness following hospital discharge (Major et al., 2016). This classical 3 round Delphi consensus study was led by researchers in the Netherlands under the supervision of Doctor Marike van der Schaaf. I was identified based on my reputation and publication history and invited to be part of a panel of ten international experts for this study. The Delphi process aimed to address research gap 2 (Table 3.1. p32) by identifying what would constitute an optimal physiotherapy intervention for survivors of critical illness and what the recommended measurement tools should be. Consensus was reached for 88.5 % of statements, resulting in production of a framework to help guide physiotherapy following hospital discharge. Specifically, the expert consensus statement which arose from this publication will go some way to guiding future work in this area both for clinicians and researchers, providing information regarding essential handover information, core outcomes and recommended physiotherapy interventions.

3.6.1 Lessons learned

The panel included a heterogeneous group of researchers and clinicians from different countries, settings, and cultural backgrounds. Although this heterogeneity might strengthen the consensus statement and its practical applicability worldwide, the variety of clinical backgrounds and context of each service provision may limit the relevance for individual units / services. Additionally, the absence of survivors of critical illness or caregivers in this expert panel was a limitation to this study because important input from other perspectives is lacking.

3.7 Research reflections and clinical take home messages

Whilst it is acknowledged that at present there is insufficient evidence to demonstrate the benefit of exercise based rehabilitation in critical care survivors (Connolly et al., 2015), a number of lessons have been learned from my publications related to research gaps 1 and 2 (Table 3.1, p32) which will help future research in this area. These papers have helped to define the population most likely to benefit from ongoing rehabilitation following hospital discharge, with results from CPET demonstrating the highest level of physical debilitation in those patients with longer stays in critical care and receiving longer periods of mechanical ventilation (Benington et al., 2012). From our results and subsequent discussions with patient groups there is also a real need to consider patient centered outcomes for further research in this area. The ability to walk further or cycle for longer is not necessarily representative of an improved health status or quality of life, with interpretation difficult without specific context for the patient. Interestingly, the findings from publications three and four did suggest positive benefits to non-physical aspects of recovery. One evolving theory is the effect of the intervention on anxiety, depression and QOL may be due to opportunity for patients to share their experiences with others in the class, thus normalising their experience. This may explain why these improvements had not been observed previously in trials where exercise was delivered individually either at home or during 1:1 sessions. This was evidenced in the trial by Batterham and colleagues (2014) which maybe surprisingly failed to demonstrate any benefit to QOL scores despite significant improvements in performance in cycle ergometry over controls at 8 weeks.

The completion of these studies has helped to develop and shape my research knowledge and skills for a number of reasons. The subsequent lessons learned were important and will hopefully improve the quality of my future work specifically in the level of detail required. The keys aspects to this are

1. Whilst the strength of my publications related to the post ICU rehabilitation programme was having a clearly defined intervention with clearly defined targets of intensity for progression (McWilliams et al., 2009; Jones et al., 2015; McWilliams et al., 2016), the lack of any direct measurement regarding activity in the control group meant the intervention data was incomplete.

2. My increased awareness of the complex interventions framework (Craig et al., 2008) has taught me that actually the post ICU rehabilitation programme had a number of additional components I had not considered which may have been having an important impact on outcomes. One such element may be the provision of group support, allowing patients to interact with others who had also been in critical care. By working within this framework for future trials I am now able to more clearly define both my intervention and the possible confounding variables which need to be controlled for or included as part of a process analysis.

3. The choice of primary outcomes lacked any real patient and public involvement (PPI) and therefore in hindsight may not have been the most appropriate measures to use. At the start of my research journey ten years

ago it was not routine practice to consult PPI groups regarding research projects and my findings help to emphasise the need to include patient perspectives in research. Subsequent feedback gained through close links with our hospital PPI group has highlighted the need for physical outcomes to be taken in perspective of a patient's previous physical ability. As an example, an improvement in walking distance can mean very different things to different people and does not always constitute a better outcome for patients. Instead, measures of quality of life and / or patient satisfaction with the programme and their recovery would be much more useful and relevant outcomes to use.

4. The findings from McWilliams et al (2016) and Jones et al (2015) suggested positive benefits to non-physical aspects of recovery in response to the rehabilitation programme. It may in fact be the effect of the intervention on anxiety, depression and QOL was due to the opportunity for patients to share experiences with others in the class, thus normalising their experience. This may explain why these improvements had not been observed previously in trials where exercise was delivered individually at home (Elliott et al., 2011).

3.8 Chapter Summary

This chapter began by introducing the long-term impact of critical illness and the need for ongoing rehabilitation following hospital discharge. I presented my first paper which evaluated the feasibility of a novel post ICU rehabilitation programme (McWilliams et al., 2009) and the development of my research in this area. Whilst

not providing any definitive answers to research gaps 1 and 2, a lot of lessons have been learned which will help in the development of future trials in this area and will be discussed in more detail in chapter 5.

Chapter 4 – Early Rehabilitation

This chapter relates to publications 6-11 presented in Table 1.1(p13) and aims to address research gaps 3 and 4 (Table 4.1) by answering the following research questions..

Table 4.1 Research gaps and associated research questions

Research Gap	Research Questions
Research gap 3. Development of a robust and measurable structure for rehabilitation delivery within critical care	What is the impact of an early and enhanced rehabilitation program for mechanically ventilated patients in a large tertiary referral, mixed-population intensive care unit? (McWilliams et al., 2014) Does the introduction of a specialist seating device reduce the time taken to first mobilise patients who have been ventilated for at least five days and at risk of ICU acquired weakness? (McWilliams et al., 2017) What are the differences between a structured early rehabilitation intervention and standard care for patients admitted to critical care and what outcomes are most appropriate for inclusion in a future definite randomised controlled trial? (Snelson et al., 2017; McWilliams et al., 2018)
Research gap 4 The identification of specific barriers to the implementation of early rehabilitation programmes and methods to overcome them	What is the current level of diffusion of early mobility practice and what are the environmental factors that may influence its practice? (Bakhru et al., 2015; Bakhru et al., 2016)

These papers all relate to the topic of early rehabilitation, specifically defined as rehabilitation which commences within critical care. Whilst my earlier research has explored methods to support long-term recovery from critical illness, I became increasingly interested in the potential for preventing or minimising the physical impact of critical illness whilst patients were still within ICU. Specifically the papers included in this chapter will aim to develop and evaluate a structured approach to rehabilitation within ICU (McWilliams et al., 2015; Snelson et al., 2017), identify barriers to its implementation and key components of successful practice (Bakhru et al., 2015; Bakhru et al., 2016) and to explore the potential to start rehabilitation at an earlier time point through the use of a specialist seating device to enable earlier transfer out of bed (McWilliams et al., 2017).

4.1 Background

With the increasing awareness of the long-term physical and psychological sequelae of critical illness, an increased focus was being placed on strategies to either prevent or minimise the physical impact of a stay in critical care. Patients admitted to critical care experience significant muscle decline, with losses of up to 25% seen for those in multi organ failure (4-6 organs) by day 10 (Puthucheary et al., 2013). The principle of early rehabilitation theorises that if rehabilitation is started earlier in the patients critical care stay, a lesser degree of muscle will have been lost and the impact of critical illness would be reduced, resulting in both a faster and more complete recovery. A study by Bailey et al (2007) demonstrated the safety and feasibility of early mobilisation within critical care a decade ago, even whilst patients were still invasively ventilated. As previously discussed in

section 2.2, evidence from small, single centre studies suggests that early physical therapy in intensive care has beneficial effects on the incidence of delirium, physical function, health related quality of life, ventilator free days, and length of stay in the ICU and hospital (Morris et al., 2008; Schweickert et al., 2009; Needham et al., 2010).

4.2 Early and structured rehabilitation

In 2012 I moved to the Queen Elizabeth hospital in Birmingham where I was appointed to a newly created clinical specialist physiotherapist post, with a specific focus on rehabilitation. Paper 6 represents the first ever study looking at the implementation of early mobilisation within a UK based critical care unit (McWilliams et al., 2015) and aims to address research gap 3 (Table 4.1, p51). The design of this novel study was challenging for a number of reasons. As previously discussed in Chapter 2, it was unclear whether improvements seen in the United States were applicable to European based structures and processes of physiotherapy delivery, or whether it was the introduction of daily physiotherapy and the focus on rehabilitation which was having a positive impact. As the standard care provided at my institution already included daily physiotherapy input, it would have been unethical to replicate previous trials by limiting physiotherapy and rehabilitation to form any control group. The challenge of any randomised controlled trial would therefore be to develop an intervention which promoted an improvement in rehabilitation delivery over and above what was already being provided. This was made even more difficult at the time (2012), as there was no definition of what constituted standard care for rehabilitation within critical care

units. Methodologically from a blinding perspective, although it would have been possible to ensure patients in the intervention and control groups were assessed and treated by different physiotherapists, this was not the case however with medical staff, nurses or other members of the MDT which may have impacted on the care provided for each group. Given the high risk of contamination between groups and the need to promote a positive change in the overall culture of the unit, a quality improvement process was therefore chosen with the aim of providing an optimal structure for rehabilitation.

The quality improvement approach encompasses a variety of methods involving a team of individuals working towards a common goal or aim (HRSA, 2011). As principal investigator for this trial the quality improvement process I chose was the 4 E's method of service improvement (see Figure 4.1). I chose this method over the traditional plan-do-study-act model due to my own familiarity with the process and reported limitations in the plan-do-study-act model when evaluating complex healthcare processes (Reed and Card, 2016).

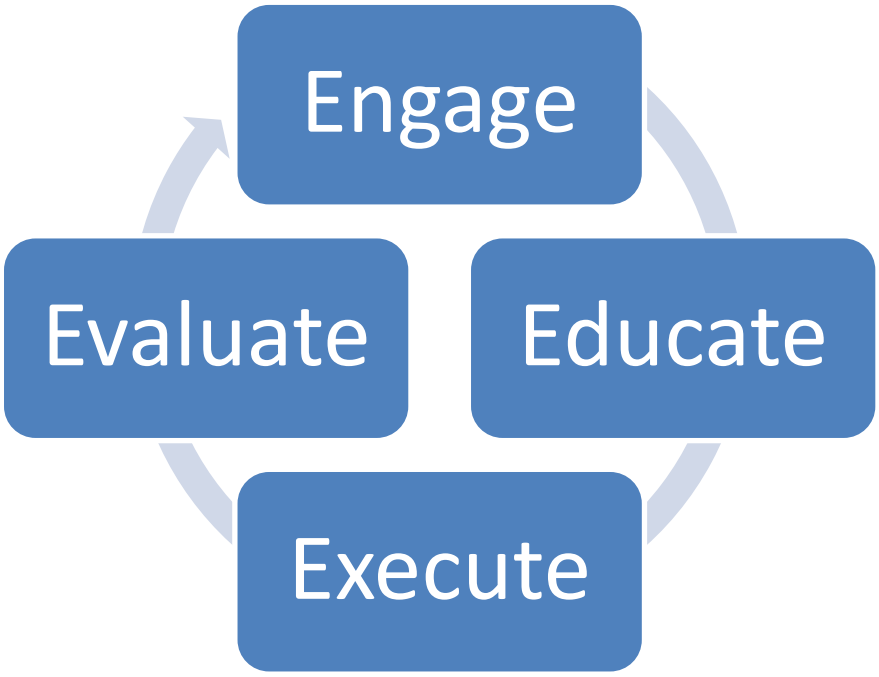

Figure 4.1 The 4 E's approach to quality improvement (Adapted from Pronovost et al, 2008)

The key first stage of the 4 E's process emphasises the need to engage with key stakeholders to identify barriers and solutions for the project goals (Pronovost et al. 2008). To this end I 'engaged' and 'educated' physiotherapy, nursing, and medical staff on the importance and benefits of early rehabilitation in ventilated patients through individual bedside training and clinical meetings. This ensured everyone had a voice and was involved in the change process. In order to 'execute' the intervention I utilised my previous knowledge and experience, coupled with recommendations from NICE CG83 to develop a pre-defined structure of rehabilitation delivery. This included the creation of a rehabilitation sub-team with a specific focus on earlier and structured rehabilitation for patients mechanically ventilated for five days or more. The intervention structure utilised

comprehensive assessments, documented rehabilitation goals and multidisciplinary ward rounds to aid communication between team members.

During the quality improvement period patients were mobilised significantly earlier in their critical care stay (6.2 vs 9.3 days, p=0.001) and achieved higher levels of mobility at the point of critical care discharge (MMS 7 vs 5, p<0.05). This was associated with a significant reduction in both ICU (16.9 vs 14.4 days; p = 0.007) and total hospital length of stay (35.3 vs 30.1 days; p < 0.01) and reduced in-hospital mortality (39% vs 28%; p < 0.05). Only a third of eligible patients were directly treated by the specific rehabilitation team, but a change in the culture of the ICU in favour of early mobility was demonstrated.

4.2.1 Lessons learned

The before-after design and the lack of blinding of the study team to the outcomes were a major weakness of the study. It is possible the results may have been subject to temporal changes and measurement bias. However, there were no other major Quality Improvement projects or service developments introduced during the study period, and consultant medical and senior nurse staffing were consistent. Additionally, no changes were made to sedation practice or weaning processes throughout the study period. The improvements seen in both the time taken to mobilise and the highest level mobility at critical care discharge are directly attributable to enhanced rehabilitation. The improvement in mobility outcomes demonstrated across all patients was likely due to an increased

awareness of early mobilisation and a transformation in culture within the whole ICU. What became particularly apparent was that the concept of early rehabilitation was not a clearly defined, one size fits all intervention.

It was at this point I became more aware of the complex interventions framework and the need for a more robust methodology for further investigating this topic. Subsequently, following completion of this study I was left with a number of questions:

1. What were the key components of the intervention and could these be replicated in other centres?

2. What constitutes 'early' rehabilitation and could we be even earlier?

3. What process measures were important to capture as potential confounding variables

4.3 Surveys of rehabilitation practice

Coupled with my drive to more clearly define the key components of an early and structured rehabilitation intervention, an increased focus was also being placed on the lack of translation of early rehabilitation research into practice. Papers 7 and 8 were completed in collaboration with International expert Dr William Schweickert from the United States (Bakhru et al., 2015; Bakhru et al., 2016) and attempted to address research gap 4 (Table 4.1, p51). I was invited to join the research group by Dr Schweickert as an expert member for Europe having been the only person

to have published a trial of early rehabilitation within the United Kingdom at the time (2014). This industry sponsored project aimed to identify current levels of rehabilitation practice, key components included in successful services and finally any barriers or restrictions to implementation. This novel project involving an international survey was the first study to explore these aspects across a large number of ICU's.

The first stage of this project included 500 critical care units across the United States of America (Bakhru et al., 2015), with the second stage then adding and comparing results from England, France and Germany (Bakhru et al., 2016). I was directly involved in designing the survey, identifying core domains and questions for inclusion within each section. We piloted the questionnaire used with a group of nurse managers for ease of completion and amended it accordingly. In order to gather sufficient data regarding early mobility practice we targeted a response of approximately 100 ICUs with early mobility protocols. Based on an estimation that 25% of ICUs would have a protocol for early mobility, we elected to survey until we reached a total of 500 ICUs from the United States. A random 10% resampling was performed 1 month after initial administration in order to assess test-retest reliability.

The survey, which achieved a 73% response rate, provided a useful insight into both current practice and barriers to implementation. Less than half (45%) of the units surveyed reported established early mobility practice. Whilst confirming the lower levels of physiotherapy provided within critical care in the United States (only

34% reporting a dedicated physiotherapist), some important information was provided regarding the key components included in those with successful early mobility programmes. Specifically, factors found to be independently associated with early mobilisation protocols were:

- A dedicated physical/occupational therapist for the critical care unit
- A written sedation protocol
- Daily multidisciplinary rounds
- Written daily goals for patients

These findings were comparable with the result from European populations (Bakhru et al., 2016), with the addition of higher intensity nursing staff ratio's also having an impact. These findings were of particular interest to my work, highlighting the importance of having a robust structure to support rehabilitation within critical care.

4.3.1 Lessons learned

An important finding from both surveys (Bakhru et al., 2015; Bakhru et al., 2016) was the substantial heterogeneity reported in both early mobility practices and barriers to implementation. Commonly cited barriers included equipment, staffing, patient and caregiver safety, and competing priorities. In ICUs without early mobilisation adoption, 78% had considered implementation but cited barriers including competing priorities and the need for further planning. What became clear was that implementation, whether through trials or quality improvement projects, must account for ICU staffing and practice patterns for success. This may have accounted for the positive results seen in my own trial (McWilliams et al.,

2015), where a key component included the identification of barriers and methods to overcome them as opposed to more recent trials which have simply aimed to increase the dose or frequency of physiotherapy (Denehy et al., 2013; Morris et al., 2016; Wright et al., 2017).

4.4 Earlier rehabilitation

Despite the now widely used terminology of ‘early rehabilitation’, no exact definition for what constitutes ‘early’ currently exists and the onset of interventions can vary by as much as 1 week (Taito et al., 2016). Additionally, patients most at risk of physical and non-physical morbidity are often too acutely unwell for active mobilisation to be commenced safely in the first few days of critical illness. For these patients the important factor may instead be the implementation of “earlier” interventions, whereby mobilisation can be initiated at a more acute stage of the patient’s illness than would previously have occurred. This supports the personalised medicine concept (NHS England, 2016), whereby treatment delivered is individualised to the patient, rather than simply focussing on a one size fits all approach. The time taken to mobilise appears to have a significant bearing on a patients short and long-term recovery. Control patients in the study by Morris et al (2008) took on average 6 days longer to mobilise out of bed for the first time compared to those receiving daily physiotherapy, with the result being longer stays in both ICU and on the wards. This was a similar finding to Schweickert and colleagues (2009), where control patients who received no physiotherapy whilst invasively ventilated, took an average of 5 days longer to mobilise out of bed and demonstrated longer duration of mechanical ventilation,

higher incidence and duration of delirium and poorer functional outcomes at the point of hospital discharge. The ability to minimise the duration and subsequently the impact of critical illness associated bedrest is therefore of paramount importance.

International recommendations regarding safety criteria have been produced to support clinicians in the decision making for commencing early rehabilitation within critical care (Hodgson et al., 2014). These guidelines were supported by a number of studies which have explored the safety of mobilisation programs within critical care, suggesting a low incidence of adverse events, even in patients who were still mechanically ventilated via either tracheostomy or endotracheal tubes (Bailey et al., 2007), and for those receiving continuous haemofiltration (Wang et al., 2014). Despite this, point prevalence surveys have demonstrated low levels of rehabilitation occurring in practice, with numerous barriers and concerns around patient safety consistently cited.

Paper 9 is a single centre, prospective before and after study evaluating the impact of introducing a specialist device to support earlier mobilisation within critical care (McWilliams et al., 2017). The Sara Combilizer (Arjo Huntleigh) is a combined chair and tilt table which can be taken completely flat to allow transfer via a sliding board (see Figure 4.2), in addition to allowing fully supported seated and standing positions to be achieved (see Figure 4.3). The chair position also has a ‘tilt in space’ recline function which allows more supportive seating positions to be achieved in comparison to standard chairs used within the ICU. I first became

aware of this device whilst presenting at an International conference in Vienna in 2010. I discovered this device had been widely used with neurological populations in Scandinavia but as yet was unavailable in the United Kingdom and had not previously been used with critically ill patients. With ongoing concerns regarding the safety of early mobilisation in the acute phases of illness, coupled with the often multiple intravenous lines and attachments for monitoring present, I hypothesised that due to the passive nature of transfer, the Sara Combilizer may facilitate earlier mobilisation than was currently possible. Although not as physiologically demanding as sitting on the edge of the bed, passive chair transfer does still elicit both a cardiovascular and respiratory exercise response (Collings and Cusack, 2015), therefore the device still had the potential to promote the desired exercise response to positional change. The aim of this study was to investigate whether the Sara Combilizer could facilitate safe and earlier mobilisation of critically ill patients at high risk of ICU acquired weakness who would otherwise be unable to get out of bed, thereby reducing time to first mobilisation (research gap 3 – Table 4.1, p51)).

Figure 4.2 The Sara Combilizer being used to transfer a patient (image supplied and permission granted for use from the copyright holder Arjo Huntleigh)

Figure 4.3 The Sara Combilizer in sitting and standing positions (images reproduced from McWilliams et al, 2016 with permission from Elsevier under the creative commons license).

As principal investigator I was responsible for all key aspects of this study, including completing the application for and obtaining funding, obtaining ethics, developing the intervention and the study protocol, as well as overall trial management. A prospective before and after design was chosen for the evaluation. The Sara Combilizer specifically targets those patients with restrictions to mobilisation and the most profound weakness in critical care. It is therefore not a device which would need to be used with all patients, meaning an RCT which mandated its use may not have been a fair representation of any potential impact. The study design allowed the use of the Sara Combilizer and mobilisation to be determined based on the individual therapists own clinical reasoning, rather than mandated as part of a standardised protocol. Additionally, I wanted to evaluate its use as a component of critical illness rehabilitation that was available for all staff within critical care, not just physiotherapists. The introduction of the device with a month of training and orientation for all staff aimed to ensure it was widely available for use and not confined to just within physiotherapy working hours.

The movement of my research to a more acute phase of the patients' illness created new ethical considerations which I had not previously encountered in my research career. The study aimed to recruit patients who were likely to lack capacity to consent due to the nature of the underlying disease process and the treatments they were receiving (e.g. sedative medications, mechanical ventilation). Due to this lack of capacity, the trial was subject to the requirements of the Mental Capacity Act 2005. Within the context of these legislative frameworks, the research was directly related to the treatment of the critical illness and it was not therefore possible to undertake this research study with comparable effectiveness

in people with capacity. As part of the ethical approval application I developed comprehensive patient and relative information leaflets, explaining the trial fully and the rationale for earlier mobilisation in this patient group. Ethical approval was granted based on receiving written informed consent from a personal consultee or Registered Medical Practitioner if no personal consultee was available. Once the patient regained mental capacity, written informed consent was gained directly for ongoing participation in the trial.

A power calculation was performed using time to first mobilise taken from pilot data based on a 2 tailed t-test, with significance level of 0.05 and an 80%power. Based on these figures and using a minimal detectable difference of a reduction of 3 days in time to first mobilise, a sample size of 30 patients in each phase (before and after introduction of Sara Combilizer) was required. Therefore, planned recruitment was for 40 patients in each phase of the study, to allow for ICU mortality and withdrawals from the trial.

The introduction of the Sara Combilizer was associated with a significant reduction in time taken to mobilise (defined as sitting out of bed) for patients ventilated ≥ 5 days (10.6 vs 13.6 days, p=0.028). To gain a more comprehensive perspective we also collected daily sequential organ failure assessment (SOFA) scores, which is a validated measure used to assess the level of organ dysfunction and mortality risk in critical care patients. Importantly, significantly higher SOFA scores were present at the point of first mobilisation in the Sara Combilizer group (5.1 vs 2.9, p=0.005).

This demonstrated patients were safely mobilised at a more acute stage of their illness and in a higher degree of organ failure than seen in the control group.

4.4.1 Lessons learned

Some baseline population differences were observed in terms of admission specialty which may have impacted on these results. The baseline data collection occurred during the summer months and included a higher proportion of trauma and neurological patients, who may have different recovery trajectories to the more medical based population in the intervention group. Despite this the illness severity scores were observed to be higher in those patients first mobilised using the Sara Combilizer, suggesting the use of such devices could facilitate earlier mobilisation than was previously seen.

4.5 Research reflections and clinical take home messages

Studies evaluating the barriers to implementation of early rehabilitation within critical care suggest the issue is multifactorial, with the overall unit culture, teamwork and communication key components required to positively create change (Parry et al., 2016; Dubb et al., 2016). Additionally, the delivery of rehabilitation within critical care is a complex process and can be affected by a number of potential confounding factors such as sedation and delirium management, weaning strategies and staffing levels to name but a few. In paper 6 I described a quality improvement project for early and structured rehabilitation. The introduction of a specialist team for rehabilitation led to a significant

improvement in mobility at ICU discharge, and this was associated with a significant reduction in ICU length of stay (LOS), ventilator days and in-hospital mortality. However, only a minority of the eligible ICU patients were treated by the team and unmeasured confounding factors may have impacted on results seen. On reflection, the use of a before and after design meant it was difficult to define on an individual patient level the constituent parts of standard and enhanced care. The rehabilitation intervention therefore required further evaluation prior to a multicentre trial.

When introduced, programmes of early rehabilitation have led to significant improvement in outcomes such as reduced weaning times, shorter ICU and hospital lengths of stay and a better functional recovery (Morris et al., 2008; Schweickert et al., 2009; Needham et al., 2010; McWilliams et al., 2015). The focus on this topic has subsequently moved from a question of 'should we' be introducing such programmes to one of are we actually harming patients if we do not (Clemmer, 2014). The cause of this lack of translation into practice has therefore become a source of much interest, with findings suggesting the causes are multifactorial and varies between nations, regions or even ICU's within the same hospital. This thesis has identified early rehabilitation to be a complex intervention, with successful implementation based on more than simply increasing the dose or frequency of physiotherapy delivery. This is particularly apparent as studies completed for units with already established physiotherapy services have failed to demonstrate the positive benefits seen in earlier trials (Denehy et al., 2013; Wright et al., 2017).

A randomised controlled trial by Denehy and colleagues (2013) evaluated the impact of enhanced rehabilitation across a continuum of patient's recovery in Australia. The intervention provided commenced within the ITU and continued to ongoing rehabilitation in the community following hospital discharge. More specifically, the intervention comprised of an increased frequency and duration of physiotherapy, aiming for 15 minutes twice daily within the ICU and up to 1 hour daily in the ward environment, with progression of exercise guided by patient exertion scores. Despite the increased intensity of physiotherapy no significant differences were observed for functional outcomes or quality of life scores, although the study failed to reach its recruitment target 150/200 and targeted adherence with the outpatient component of the intervention was poor (41%). Additionally, no measures regarding specific physiotherapy activity which was delivered within critical care were provided (e.g. proportion of active rehabilitation sessions), preventing any comparison with other previously published interventions.

The recently published EPICC trial (Wright et al., 2017) evaluated the impact of an increased dose of physiotherapy provision within two UK based ICU's. 308 patients were recruited to the trial over a 2 year period. Participants randomised to the intervention group had a target of 90 minutes of physical rehabilitation, in comparison to a target of 30 minutes in the control arm, although actual rehabilitation delivered fell significantly short of these targets (23 mins in the intervention group and 13 minutes in the control group). No differences were observed in time to commence rehabilitation and actual rehabilitation delivered

was broadly similar between groups. No significant differences were seen between groups for any of the physical, non-physical or clinical outcomes assessed.

Both studies (Denehy et al., 2013; Wright et al., 2017) describe the large degree of heterogeneity of critical care populations to be a significant limitation and discuss the need for future research to tailor rehabilitation to individual patient needs rather than a one size fits all dose approach. The lack of any measures of overall rehabilitation service delivery such as open forums for MDT rounds and collaborative goal setting may have been a limitation. Given the complex nature of early rehabilitation in patients with multi-organ failure, these rounds provide team members with the opportunity to discuss the patients' rehabilitation in the context of medical stability, any current plan for weaning of sedation and respiratory support, management of delirium and to highlight other team member tasks which may require completion. This further supports the argument that to be successful programmes of early rehabilitation need to be considered as complex interventions which are adaptable to meet individual patient needs.

Complex interventions are usually described as interventions that contain several interacting components (Craig et al., 2008). Specific dimensions which make an intervention complex include:

1. Number of and interactions between components within the experimental and control interventions
2. Number and difficulty of behaviours required by those delivering or receiving the intervention

3. Number of groups or organisational levels targeted by the intervention
4. Number and variability of outcomes
5. Degree of flexibility or tailoring of the intervention permitted

In order to ensure effective and established behavioural change, clinicians need to explore the structure and culture within critical care units. Strategies such as daily MDT ward rounds, team meetings, collaborative inter-professional goal setting and visible goal targets are all excellent tools to support changes in practice. Although apparently simple solutions, these strategies do still have resource implications and take clinicians away from frontline care. Within the current budget restraints of the NHS, it is perhaps understandable that these aspects of care are not prioritised. A number of studies have used a quality improvement approach for the implementation of early and structured rehabilitation within critical care. In my own study of implementing early and structured rehabilitation (McWilliams et al., 2015) I used the 4 E's methodology described in chapter 4 and shown in Fig 4.2. The key first stage to this process emphasises the need to engage with key stakeholders to identify barriers and solutions for the project goals (Pronovost et al., 2008). As previously discussed, the concept of implementing early rehabilitation programmes is not a 'one size fits all' approach and the specific barriers to implementation may be unique to each individual ICU. Underpinning the engagement process should be a focus on the importance of collaborative team working, ensuring everyone has a voice and is involved in the change process.

Commencing mobilisation is however only the start of the rehabilitation journey and any protocol developed should also provide a structure or framework to

empower healthcare professionals to progress activity and ensure ongoing collaboration between team members. Papers 7 (Bakhru et al., 2015) and 8 (Bakhru et al., 2016) provided useful insights into key components of practice which may be required to support early rehabilitation programmes. The presence of a dedicated physiotherapist (odds ratio 3.34; $p<0.01$), MDT ward rounds (odds ratio 2.31, $p<0.01$) and daily goal setting for rehabilitation (odds ratio 2.17, $p=0.04$) were significantly associated with the presence of established early mobility practice within the ICU's surveyed. These findings were a major contributing factor to key recommendations included in the recently published NICE quality standard, QS158 - rehabilitation after critical illness (NICE, 2017) which also represents paper 13 included in this thesis. Following my involvement in the original NICE guideline CG83 (NICE, 2009) I was also successful in gaining a place as the physiotherapy representative on the guideline development group for the quality standard (NICE, 2017).

NICE quality standards aim to set priority areas for quality improvement in healthcare. Each quality standard provides:

- A set of statements to help improve quality
- Information on how to measure progress.

Based on my research findings in this area, the decision was made to include key structural components for rehabilitation as a key recommendation within NICE QS158 (paper 13), specifically the need for early and regularly updated

multidisciplinary team goals within critical care. The setting of these goals is underpinned by the need to establish an open forum for MDT communication, with multidisciplinary rounds one such example where the patient's plan of care can be discussed formally as a team and tasks prioritised. There is evidence to support the initiation of patient care rounds in other areas of care, where they have been associated with positive patient outcomes (Stone et al., 2011). The development of shared goals is crucial for fostering team commitment and a shared sense of identity which makes effective teamwork possible. Conversely, failure to develop consistent treatment goals among ICU staff has been identified as a key source of intra-team conflict, which, in turn, is perceived to impact on outcomes such as decreased quality of patient care, staff burnout and wasted resources (Danjoux Meth et al., 2009). Given the complex nature of early rehabilitation in patients with multi organ failure, these rounds provide team members with the opportunity to discuss the patients' rehabilitation in the context of medical stability, any current plan for weaning of sedation and respiratory support, management of delirium and to highlight other team member tasks which may require completion (Bakhru et al., 2016).

4.6 Future Research

Paper 10 aims to address research gap 3 (Table 4.1, p51) and presents a trial protocol evaluating the feasibility of delivering earlier and enhanced rehabilitation for patients mechanically ventilated for ≥5 days. The proposed feasibility trial also aims to assess the impact on possible long term outcome measures for use in a future definitive trial (Snelson et al., 2017). The protocol is included in this thesis

as it demonstrates the future plans for my research. This represents the culmination of what I have learnt regarding early and structured rehabilitation from papers 6-12, as well as my development as a researcher and what I have learnt from a methodological perspective from all of the included papers.

As a feasibility trial, this study is more focussed on the acceptability, compliance, recruitment, retention and delivery of the intervention. The feasibility trial will also allow evaluation of potential outcome measures for any future definitive trial, identifying any smaller than expected effect sizes that could have been predicted by thorough piloting (Craig et al., 2008). The development of this protocol represents the culmination of knowledge gained from the previous papers in this chapter and the evolving evidence base for critical care rehabilitation.

Key research learning points that have been included are:

- Clearly defining the population under study
- Dealing with the ethics of completing research in patients who at the time of inclusion lack capacity and are therefore unable to provide informed consent
- A complex evaluation of the intervention and all potential components
- Adding defined measures of rehabilitation activity over and above therapy time alone
- Increasing the range of outcomes measured to include both physical and non-physical factors

- Increasing the length of follow up measures to gain a greater insight into longer-term recovery.

For this feasibility trial we targetted patients admitted to critical care and ventilated for ≥ 5 days. Although representing only 5% of all ICU admissions, patients with "persistent critical illness" consume significant resource and require dedicated future research (Iwashyna et al., 2016). This population was specifically chosen to target patients most at risk of ICU acquired weakness, aiming to find the balance between excluding those with short stays and expected faster trajectories of recovery, whilst still ensuring rehabilitation could be commenced early enough to be effective. In targeting a longer stay critical care population it is acknowledged that other factors may have an impact on overall outcome and recovery. Older ICU survivors in particular suffer prolonged and persistent decline in cognitive and physical function with those with a length of stay more than 2 weeks at highest risk for 1-year mortality and disability (Herridge et al., 2016). One reason for this may be due to age-related sarcopenia, where individuals who are physically inactive can lose a significant amount of muscle mass after the age of 30 years, with losses increasing to 1-2% per year from the age of 50 (Griffiths, 1996). Additionally the severity of organ dysfunction on admission to critical care can impact on overall outcome, with mortality significantly higher in those patients with higher SOFA scores (Ferreira et al., 2001). On randomisation participants will therefore be stratified into four groups, based on the combinations of age (<50 versus ≥50 years) and SOFA score (<9 versus ≥9).

From an outcomes perspective, Paper 10 will evaluate the feasibility of the enhanced rehabilitation intervention in terms of the recruitment process, compliance and differentiation from standard care. This feasibility trial will also evaluate a range of clinical and patient-reported outcome measures to aid selection of the most appropriate primary outcome measure for a definitive trial, providing estimates of variance for sample size calculation for a definitive randomised controlled trial. Definitive randomised controlled trials follow on from feasibility testing and aim to evaluate the intervention for clinical and cost effectiveness, as well as gain a greater insight into the change process (Craig et al., 2008). Within the feasibility trial (Snelson et al., 2017) the analysis of the feasibility of the recruitment process will be the proportion of eligible patients who are recruited and then complete all study assessments. Within a single centre, there is a significant risk of changing practice within the control group over the course of the study. Adherence and differentiation of groups will be assessed by a number of key process measures. These were derived from key recommendations in NICE CG83 (NICE, 2009) and findings from my previous research in this area (McWilliams et al., 2015; Bakhru et al., 2015; Bakhru et al., 2016) and include

- Having a named keyworker for rehabilitation
- Completion of a comprehensive baseline assessment
- Weekly goal setting meetings
- Individualised and documented rehabilitation plans
- Time to first mobilise
- Highest level of mobility achieved within critical care
- Proportion of rehabilitation sessions
- Proportion of and reasons for any missed therapy sessions

4.7 Feasibility Trial Results

The feasibility trial discussed in section 4.6 above was completed and published (McWilliams et al., 2018) during the completion of this thesis and has therefore been included as paper 11. Recruitment to the trial was excellent, with 103/128 (80%) eligible patients recruited over the study period. Patients receiving the enhanced rehabilitation programme mobilised significantly earlier (8 vs 10 days, $p=0.035$), at a more acute stage of their illness (SOFA score 6 vs 4, $p<0.05$) and reached a higher level of mobility at the point of critical care discharge (MMS 7 vs 5, $p<0.01$). It is important to acknowledge that this study was completed on the same unit which underwent a quality improvement project around early mobilisation published in paper 6 (McWilliams et al., 2015), with control patients maintained the increased level of mobility at critical care discharge previously seen (MMS = 5). The results of paper 11 therefore represent a further enhanced level of mobility; specifically over 70% of patients in the intervention arm could walk > 30 metres by the point of critical care discharge.

A comparison of the 2 arms of the study demonstrated confirmation of some earlier hypotheses discussed. The improvements seen in the intervention group were achieved without any significant increase in therapy dosage or duration (35.4 vs 38.3 mins, $p=0.1577$). However, important structural differences were noted with regards to completion of comprehensive assessments, goal setting, regular MDT reviews and fewer missed rehabilitation sessions. This supports the findings from papers 7 and 8 (Bakhru et al., 2015; Bakhru et al., 2016) highlighting the importance of having a robust and measurable structure for rehabilitation. These

findings will go some way to addressing research gap 3 (Table 2.1, p29, 30) and help to provide a framework for implementation of rehabilitation in other centres as part of any future trials as well as providing a useful insight into key process measures for rehabilitation.

This study did however have some important limitations, the biggest of which being the lack of blinding and potential for contamination across groups. Due to the size of our critical care unit it was possible to ensure patients in the intervention and control groups were assessed and treated by different physiotherapists. This was not the case however with medical staff, nurses or other members of the MDT which may have impacted on the care provided for each group. Another significant limitation was the degree of missing data and the high loss to follow up rate. This occurred despite the presence of dedicated research nurses for data collection and was related to a number of factors including a reduced cognitive status both within critical care and on return to the ward. Missing data limits the precision of the results and could be a source of bias, although the rate of non-completion was similar for outcomes between groups and similar to completion rates seen in other trials assessing critical care survivors following hospital discharge (Denehy et al., 2013; Wright et al., 2017).

4.8 Chapter Summary

This chapter began by introducing the concept of starting rehabilitation whilst patients were still in ICU in order to minimise or prevent physical morbidity

associated with critical illness. The papers included in this chapter attempt to address research gaps 3 and 4 (table 4.1, p51). I presented a quality improvement project evaluating the impact of early and structured rehabilitation within critical care (McWilliams et al., 2014) and discussed the changing focus of research towards methods to overcome barriers to the implementation of similar programmes in other ICU's. This chapter concluded with a summary of lessons learned and described results from a recently published trial (McWilliams et al., 2018) which has helped to address the ongoing gaps within the evidence.

Chapter 5 – Discussion and Conclusions

This chapter provides an overview of this thesis. The overall methodological strengths and limitations and novel aspects of the papers included in this thesis are discussed. Finally, overall learning points from this thesis are discussed with regards to future research opportunities and challenges in order to continue to develop the evidence base for critical illness rehabilitation and recovery.

5.1 Strengths and Limitations of this Thesis

The papers included in this thesis have a number of strengths. I have presented a range of studies evaluating the impact of rehabilitation for patients admitted to critical care at various different stages of their recovery. The studies included have ecological validity as they were conceived and designed in the real world environment of the NHS as a practicing expert NHS clinician, thus having excellent transferability to the wider NHS although may be limited in terms of International transferability. A variety of methodologies have been included to answer a range of research questions. The thesis summarises my development from a novice to expert clinician and as a researcher, including collaborations with well-respected international experts in the field of critical care rehabilitation. A number of novel aspects have been included throughout this thesis and are summarized in section 5.2. My work in post ICU rehabilitation has followed the complex interventions framework, moving from initial development of a novel post ICU rehabilitation programme to feasibility testing and then evaluation in a large, multi-centre randomized controlled trial. Paper 6 (McWilliams et al., 2015) remains the only successful trial of early rehabilitation within critical care in the UK. The quality improvement process and structure for rehabilitation delivery used in this trial has

provided a framework for clinicians to develop similar rehabilitation services nationally. The positive results seen in this project in comparison to other recent randomized controlled trials of early rehabilitation (Denehy et al., 2013; Wright et al., 2017) have helped to define early rehabilitation as a complex intervention and provide greater insight into the most appropriate format for a future definitive randomized controlled trial.

A number of limitations were also present in the papers included in this thesis, each of which has helped to refine my research questions and develop my research expertise. These have been discussed in more detail for the included papers in sections (3.2.1, 3.4.1, 3.5.1, 3.6.1, 4.2.1, 4.3.1, 4.4.1). This thesis has highlighted the challenges of evaluating complex interventions within healthcare and the need to fully understand standard care and potential confounding variables. Moving forward the key lessons learned from this thesis will help to develop a robust RCT clinical trial for both early rehabilitation and post ICU rehabilitation programmes.

5.2 Novel aspects of this thesis

To my knowledge, the papers included in this thesis represent the first studies to investigate

- The feasibility of a structured exercise in the form of a post ICU rehabilitation programme for critical care survivors
- Evaluate the feasibility of CPET as a measure of physical fitness in survivors of critical illness

- A quality improvement project of early and structured rehabilitation within critical care within the UK
- An international survey of early rehabilitation practice across four countries and 951 ICU's

5.3 Future research

It is important to acknowledge at the moment there is insufficient evidence to demonstrate benefit of rehabilitation either within the ICU or following discharge. However, based on the findings from this thesis several recommendations can be made as to where future research should be focused to further enhance our understanding around the value of rehabilitation following critical illness. The plans for future research related to early rehabilitation have been discussed in detail with reference to Paper 10 (Snelson et al., 2017) and 11(McWilliams et al., 2018) in section 4.6 and 4.7. The message from recent studies in this area is the key to success involves implementing changes in structure and culture, rather than simply increasing the dose of physiotherapy. Ultimately future studies should evaluate early rehabilitation as a complex intervention and may benefit from using a pragmatic, stepped wedge randomised controlled trial design. As the intervention requires a cultural change within the unit, individual randomisation at a patient level would not possible and due to the high degree of heterogeneity of intensive care units a stepped wedge approach would appear more appropriate than cluster randomisation of units. It would be essential to embed a thorough process evaluation as part of any future multicentre study to identify unit differences and potential confounding factors. It is hoped the results from paper 11

(McWilliams et al., 2018) will now help to inform the optimal structure for rehabilitation delivery and most appropriate primary outcome for evaluation.

From a post ICU rehabilitation perspective, despite a small number of randomised controlled trials looking at the effects of post intensive care rehabilitation strategies, at present it is unclear as to the most appropriate method of delivering and evaluating such programmes. Despite positive early results in terms of an improved QOL seen with the use of a self-help manuals by Jones et al (2003), this recovery appeared incomplete and even at 6 months post discharge patients still had the equivalent QOL to populations with a severe chronic illness. Subsequent reviews of self-help programmes in conjunction with intensive care follow up clinics (Cuthbertson et al., 2009) and home based rehabilitation (Elliott et al., 2011) have demonstrated no benefit over standard care in terms of physical function or QOL. Given the potential significant benefits seen by the studies into hospital based rehabilitation classes, both in terms of physical function assessed using the 6MWT (McWilliams et al., 2009) and physical components of the SF36 (Jones et al., 2015; McWilliams et al., 2016), a more detailed analysis of these interventions would appear appropriate.

In order to fully evaluate the impact of the post ICU rehabilitation programme ultimately a multi-centre trial is required and planned. Using the lessons learned from previous studies in this area (McWilliams et al., 2009; Jones et al., 2015; Major et al., 2016; McWilliams et al., 2016) a pilot phase should be embedded into a multi-centre RCT evaluating the specific impact of the post ICU rehabilitation programme on QOL of survivors of critical illness. The methodology in my previous

RCT (McWilliams et al., 2016) contained a number of flaws, as discussed on pages 39 and 40, which may have biased the results seen. Most notably significant baseline group differences were observed with regards to critical care length of stay and duration of mechanical ventilation. It is not known what impact this may have had on the trajectory of recovery and, as no further follow-up was completed other than 3 months this could not be explored further. Results from my previous work in this area (Benington et al., 2012; McWilliams et al., 2016) suggest future RCT's should include stratified randomisation, specifically related to age and length of stay, to control for variables which may impact on recovery rates seen. Additionally, when assessing physical outcomes it is essential to monitor level of activity in both groups, rather than simply class attendance in the intervention group, in order to fully appreciate any changes in outcome according to level of activity. As recommended through my subsequent patient and public involvement activity with our critical care pathfinders group, the patient perspective on recovery is vital when evaluating the impact of these programmes. The use of a QOL score as a primary outcome coupled with the inclusion of a qualitative analysis will give a much greater insight into the patients' recovery, ensuring this is appropriate and meaningful for them as an individual as well as the population as a whole.

5.4 Conclusions

In conclusion, the research presented in this thesis demonstrates the positive role of rehabilitation in supporting recovery from critical illness. Limitations of the current evidence may be complemented through definitive randomised controlled trials to further investigate both short and long term outcomes. In the short term,

early and enhanced rehabilitation on the ICU has been demonstrated to have beneficial effects on muscle strength, physical function, health-related quality of life, ventilator-free days and length of stay. The focus on research in this area has therefore moved from evaluation to implementation with future studies planned in this area. From a longer term perspective, there is also an opportunity to build on my current work through mixed methods research. This would help to further evaluate both physical and non-physical outcomes, as well as provide a greater understanding and insight into patients' recovery.

References

Bailey, P., Thomsen, G.E., Spuhler, V.J., Blair, R., Jewkes, J., Bezdjian, L., Veale, K., Rodriquez, L., Hopkins, R.O. (2007) 'Early activity is feasible and safe in respiratory failure patients.' *Critical Care Medicine,* 35(1) pp. 139-145.

Bakhru, R.N., Wiebe, D.J., McWilliams, D.J., Spuhler, V.J., Schweickert, W.D. (2015) 'An Environmental Scan for Early Mobilization Practices in United States Intensive Care Units.' *Critical Care Medicine*, 43(11) pp. 2360-2369.

Bakhru, R., McWilliams, D.J., Wiebe, D.J., Spuhler, V.J., Schweickert, W.D. (2016) 'Intensive Care Unit Structure Variation and Implications for Early Mobilization Practices: An International Survey.' *Annals of the American Thoracic Society,* 13(9):pp. 1527-37.

Batterham AM, Bonner S, Wright J, Howell SJ, Hugill K, Danjoux G (2014) 'Effect of supervised aerobic exercise rehabilitation on physical fitness and quality of life in survivors of critical illness: an exploratory minimized controlled trial (PIX study).' *Br J Anaesth*, 113(1) pp. 130-7.

Benington, S., McWilliams, D., Eddleston, J., Atkinson, D. (2012) 'Exercise testing in survivors of intensive care--is there a role for cardiopulmonary exercise testing?' *Journal of Critical Care*, 27(1) pp. 89-94.

Borg, GA. (1982) 'Psychophysical bases of perceived exertion.' *Medicine and Science in Sports and Exercise*, 14, pp377-81.

Børsheim, E., Bui, Q-U.T., Tissier, S., Kobayashi, H., Ferrando, A.A., Wolfe, R.R. (2008) 'Effect of amino acid supplementation onmuscle mass, strength and physical function in the elderly.' *Clin Nutr,* 27(2) pp. 189–95.

Brower, R.G. (2009) 'Consequences of bed rest.' *Critical Care Medicine*, 37(10 suppl) S422-S428.

Brummel, N.E., Balas, M.C., Morandi, A., Ferrante, L.E., Gill, T.M., Ely, E.W. (2015) 'Understanding and reducing disability in older adults following critical illness.' *Crit Care Med*, 43(6) pp. 1265–75.

Cheung, A.M., Tansey, C.M., Tomlinson, G., Diaz-Granados, N., Matte, A., Barr, A., Mehta, S., Mazer, C.D., Guest, C.B., Stewart, T.E., Al-Saidi, F., Cooper, A.B., Cook, D., Slutsky, A.S., Herridge, M.S, for the Canadian Critical Care Trials Group. (2006) 'Two year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome.' *Am J Respir Crit Care Med,* 174(5) pp. 538–44.

Chiang, L.L., Wang, L.Y.,Wu, C.P.,Wu, H.D.,Wu, Y.T. (2006) 'Effects of physical training on functional status in patients with prolonged mechanical ventilation.' *Phys Ther*, 86(9) pp. 1271–81

Clemmer, T.P. (2014) 'Why the Reluctance to Meaningfully Mobilize Ventilated Patients? "The Answer My Friend Is Blowin' in the Wind"' *Critical Care Medicine,* 42(5) pp. 1308–1309

Collings, N., Cusack, R. (2015) 'A repeated measures, randomized cross-over trial, comparing the acute exercise response between passive and active sitting in critically ill patients.' *BMC Anesthesiol,* 15:1 [online] [Accessed on 20th September 2017] DOI: 10.1186/1471-2253-15-1.

Connolly B; Salisbury L; O'Neill B; Geneen L; Douiri A; Grocott MP; Hart N; Walsh TS; Blackwood B; (2015) 'Exercise rehabilitation following intensive care unit discharge for recovery from critical illness.*' Cochrane Database Syst Rev*. (6):CD008632 (ISSN: 1469-493X)

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., Petticrew, M. (2008) 'Developing and evaluating complex interventions: the new Medical Research Council guidance.' *BMJ*, 337:a1655 [online] [Accessed on 20th September 2017] DOI: 10.1136/bmj.a1655

CSP. (2010) Physiotherapy Research Priority Project 2010 Prioritised research topics – Cardiorespiratory and Medical Rehabilitation. Unknown place of publication: Chartered Society of Physiotherapy. [online] [Accessed on 22nd December 2017] http://www.csp.org.uk/sites/files/csp/secure/csp_prpp2010_cmr_top%20topics.pdf

Cuthbertson, B.H., Rattray, J., Campbell, M.K., Gager, M., Roughton, S., Smith, A., Hull, A., Breeman, S., Norrie, J., Jenkinson, D., Hernandez, R., Johnston, M., Wilson, E., Waldmann, C., McDonald, A., McPherson, G., Ramsay, C.R., Vale, L., Pflanz-Sinclair, C., Wildsmith, J.A., Rose, S., Williams, B., Walsh, T. (2009) 'The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial.' *British Medical Journal.* 339:b3723 [online] [Accessed on 20th September 2017] DOI: 10.1136/bmj.b3723

Daffurn, K., Bishop, G.F., Hillman, K.M., Bauman, A. (1994) 'Problems following discharge after intensive care.' *Intensive & Critical Care Nursing,* 10 (4) pp.244-51.

Danjoux Meth, N., Lawless, B., Hawryluck, L. (2009) 'Conflicts in the ICU: perspectives of administrators and clinicians.' *Intensive Care Med*, 35(12) pp. 2068-77.

Denehy, L., Skinner, E. H., Edbrooke, L., Haines, K., Warrillow, S., Hawthorne, G., Gough, K., Hoorn, S.V., Morris, M.E., Berney, S. (2013)' Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up.' *Critical Care*, 17(4) R156. [online] [Accessesd 20th September 2017] DOI: 10.1186/cc12835.

Department of Health [DoH]. (2005) *Quality Critical Care*. London: DoH.

Desai, S., Law, T., Needham, D. (2011) ‘Long-term complications of critical care.’ *Critical Care Medicine,* 39(2) pp. 371–379.

Dowdy, D., Eid, M., Sedrakyan, A., Mendez-Tellez, P.A., Pronovost, P.J., Herridge, M.S., Needham, D.M. (2005) ‘Quality of life in adult survivors of critical illness: a systematic review of the literature.’ *Intensive Care Med*, 31(7) pp. 611–620.

Dubb, R., Nydahl, P., Hermes, C., Schwabbauer, N., Toonstra, A., Parker, A.M., Kaltwasser, A., Needham, D.M. (2016) ‘Barriers and strategies for early mobilisation of patients in intensive care units.’ *Ann Am Thorac Soc*, 13(5) pp. 724-730.

Elliott, D., McKinley, S., Alison, J., Aitken, L., King, M., Leslie, G., Kenny, P., Taylor, P., Foley, R., Burmeister, E. (2011) ‘Health-related quality of life and physical recovery after a critical illness: a multi-centre randomised controlled trial of a home-based physical rehabilitation program.’ *Critical Care.* 15:R142. [online] [Accessed on 20th September 2017] DOI: 10.1186/cc10265.

Esteban, A., Frutos-Vivar, F., Muriel, A., Ferguson, N.D., Peñuelas, O., Abraira, V., Raymondos, K., Rios, F., Nin, N., Apezteguía, C., Violi, D.A., Thille, A.W., Brochard, L., González, M., Villagomez, A.J., Hurtado, J., Davies, A.R., Du, B., Maggiore, S.M., Pelosl, P., Soto, L., Tomicic, V., D'Empaire, G., Matamis, D., Abroug, F., Moreno, R.P., Soares, M.A., Arabi, Y., Sandi, F., Jibaja, M., Amin, P., Koh, Y., Kuiper, M.A., Bülow, H.H., Zeggwagh, A.A, Anzueto, A.(2013) ‘Evolution

of mortality over time in patients receiving mechanical ventilation.' *Am J Respir Crit Care Med*, 188(2) pp. 220-30.

Ferreira, F.L., Bota, D.P., Bross, A., Mélot, C., Vincent, J.L. (2001) 'Serial evaluation of the SOFA score to predict outcome in critically ill patients.' *JAMA.* 286(14) pp. 1754-8.

Garnacho-Montero, J., Amaya-Villar, R., Garcia-Garmendia, J.L., Madrazo-Osuna, J., Ortiz-Leyba, C. (2005) 'Effect of Critical Illness Polyneuropathy on the Withdrawal From Mechanical Ventilation and the Length of Stay in Septic Patients.' *Critical Care Med*, 33(2) pp. 349-354

Griffiths, J.A., Barber, V,S., Cuthbertson, B.H., Young, J.D. (2006) 'A national survey of intensive care follow-up clinics.' *Anaesthesia,* 61(10) pp. 950-955.

Griffiths, J., Hatch, R.A., Bishop, J., Morgan, K., Jenkinson, C., Cuthbertson, B.H., Brett, S.J. (2013) 'An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study.' *Critical Care* 17: R100. [online] [Accessed 20th September 2017] DOI: 10.1186/cc12745

Griffiths, R.D. (1996) 'Muscle mass, survival, and the elderly ICU patient.' *Nutrition*, 12(6) pp. 456–8.

Griffiths, R.D., Jones, C. (2007) ‘Seven lessons from 20 years of follow up of intensive care unit survivors.’ *Curr Opin Crit,* 13(5) pp. 508–513.

Griffiths, R.D., Hall, J.B. (2010) ‘Intensive care unit-acquired weakness.’ *Crit Care Med*, 38(3) pp. 779–787.

Hermans, G., De Jonghe, B., Bruyninckx, F., Van den Berge, G. (2008) ‘Clinical review: critical illness polyneuropathy and myopathy.’ *Crit Care*, 12(6): 238. [online] [Accessed on 20th September 2017] DOI: 10.1186/cc7100

Herridge, M,. Cheung, A,. Tansey, C,. Matte-Martyn, A,. Diaz-Granados, N., Al-Saidi, F., Cooper, A., Guest, C., Mazer, C., Mehta, S. (2003) ‘One-year outcomes in survivors of the acute respiratory distress syndrome.’ *N England J Med,* 348(8) pp. 683–693.

Herridge, M.S., Tansey, C.M., Matté, A., Tomlinson, G., Diaz-Granados, N., Cooper, A., Guest, C.B., Mazer, C.D., Mehta, S., Stewart, T.E., Kudlow, P., Cook, D., Slutsky, A.S., Cheung, A.M. Canadian Critical Care Trials Group. (2011) ‘Functional disability 5 years after acute respiratory distress syndrome.’ *N Engl J Med*, 364(14) pp. 1293-1304.

Herridge, M.S., Chu, L.M., Matte, A., Tomlinson, G., Chan, L., Thomas, C., Friedrich, J.O., Mehta, S., Lamontagne, F., Levasseur, M., Ferguson, N.D., Adhikari, N.K., Rudkowski, J.C., Meggison, H., Skrobik, Y., Flannery, J., Bayley,

M., Batt, J., Santos, C.D., Abbey, S.E., Tan, A., Lo, V., Mathur, S., Parotto, M., Morris, D., Flockhart, L., Fan, E., Lee, C.M., Wilcox, M.E., Ayas, N., Choong, K., Fowler, R., Scales, D.C., Sinuff, T., Cuthbertson, B.H., Rose, L., Robles, P., Burns, S., Cypel, M., Singer, L., Chaparro, C., Chow, C.W., Keshavjee, S., Brochard, L., Hebert, P., Slutsky, A.S., Marshall, J.C., Cook, D., Cameron, J.I. (2016) 'The RECOVER program: disability risk groups & one year outcome after ≥7 days of mechanical ventilation.' *Am J Respir Crit Care Med*, 194(7) pp. 831–44.

Hodgson, C.L., Stiller, K., Needham, D.M., Tipping, C.J., Harrold, M., Baldwin, C.E., Bradley, S., Berney, S., Caruana, L.R., Elliott, D., Green, M., Haines, K., Higgins, A.M., Kaukonen, K.M., Leditschke, I.A., Nickels, M.R., Paratz, J., Patman, S., Skinner, E.H., Young, P.J., Zanni, J.M., Denehy, L., Webb, S.A. (2014) 'Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults.' *Crit Care,* 18(6) pp. 654–9.

Hopkins, R.O., Weaver, L.K., Collingridge, D., Parkinson, R.B., Chan, K.J., Orme, J.F. Jr. (2005) 'Two year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome.' *Am J Respir Crit Care Med*, 171(4) pp. 340–347.

Intensive Care National Audit and Research Centre. Case Mix Programme Case mix and Outcome Summary Statistics 2016–17. Available from https://www.icnarc.org/DataServices/Attachments/Download/7a5f8f69-5542-e811-80ec-1402ec3fcd79 (Accessed 7 June 2018)

Iwashyna, T.J., Ely, E.W., Smith, D.M., langa, K.M. (2010) 'Long-term cognitive impairment and functional disability among survivors of severe sepsis.' *JAMA*, 304(16) pp. 1787-1794.

Iwashyna, J., Hodgson, C., Pilcher, D., Bailey, D., van Lint, A., Chavan, S., Bellomo, R. (2016) 'Timing of onset and burden of persistent critical illness in Australia and New Zealand: a retrospective, population-based observational study.' *Lancet Respir Med*, 4(7) pp. 566–73.

Jones, C., Griffiths, R.D. (2000) 'Identifying post intensive care patients who may need physical rehabilitation.' *Clinical Intensive Care*, 11(1) pp. 43-46.

Jones, C., Skirrow, P., Griffiths, R.D., Humphris, G.H., Ingleby, S., Eddleston, J., Waldmann, C., Gager, M. (2003) 'Rehabilitation after critical illness: A randomised, controlled trial.' *Critical Care Medicine*, 31(10) pp. 2456-2461.

Jones, C., Eddleston, J., McCairn, A., Dowling, S., McWilliams, D., Coughlan, E., Griffiths, R.D. (2015) 'Improving rehabilitation following critical illness through outpatient physiotherapy classes and essential amino acid supplement: a randomised, controlled trial.' *Journal of critical care*, 30(5) pp. 901-7.

Karvonen, MJ. Kentala, E. Mustala, O. (1957) 'The effects of training on heart rate; a longitudinal study.' *Annales Medicinae Experimentalis et Biologiae Fenniae*. 35, pp307-315.

Kaukonen, K., Bailey, M., Suzuki, S., Pilcher, D., Bellomo, R. (2014) 'Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012.' *JAMA*, 311(13) pp. 1308-16.

Major, M.E., Kwakman, R., Kho, M., Connolly, B., McWilliams, D., Denehy, L., Hanekom, S., Patman, S., Gosselink, R., Jones, C., Nollet, F., Needham, D.M., Engelbert, R.H., van der Schaaf, M. (2016) 'Surviving critical illness: what is next? An expert consensus statement on physical rehabilitation after hospital discharge.' *Critical Care*. 20(1):354 [online] [Accessed on 20th September 2017] DOI: 10.1186/s13054-016-1508-x

McWilliams, D.J., Pantelides, K.P. (2008) 'Does Physiotherapy led early mobilisation affect length of stay on ICU.' *ACPRC Journal*, 40, December, pp. 5-11

McWilliams, D.J., Atkinson, J.F.D., Conway, D.H. (2009) 'The impact and feasibility of a physiotherapy led, exercise based rehabilitation programme for intensive care survivors.' *Physiotherapy Theory and Practice*, 25(8) pp. 566-71

McWilliams, D., Weblin, J., Atkins, G., Bion, J., Williams, J., Elliott, C., Whitehouse, T., Snelson, C. (2015) 'Enhancing rehabilitation of mechanically ventilated patients in the intensive care unit: a quality improvement project.' *J Crit Care*, 30(1) pp. 13–8.

McWilliams, D., Benington, S., Atkinson, D. (2016) 'Outpatient based physical rehabilitation for survivors of prolonged critical illness: A randomised controlled trial.' *Physiotherapy Theory and Practice*, 32(3) pp. 179-190.

McWilliams, D.J., Atkins, G., Hodson, J., Boyers, M., Lea, T., Snelson, C. (2016) 'Feasibility and reliability of the Manchester Mobility Score as a measure of physical function within the Intensive Care Unit.' *ACPRC Journal*, 48, January, pp. 26-33.

McWilliams, D., Atkins, G., Hodson, J., Snelson, C. (2017) 'The Sara Combilizer as an early mobilisation aid for critically ill patients: A prospective before and after study.' *Australian Critical Care*. 30(4) pp. 189-195.

McWilliams, D., Jones, C., Atkins, G., Hodson, J., Whitehouse, T., Veenith, T., Reeves, E., Cooper, L., Snelson, C. (2018) Earlier and enhanced rehabilitation of mechanically ventilated patients in critical care: A feasibility randomised controlled trial. *Journal of critical care. Apr (44). pp. 407-412*

Morris, P., Goad, A., Thompson, C., Taylor, K., Harry, B., Passmore, L., Ross, A., Anderson, L., Baker, S., Sanchez, M., Penley, L., Howard, A., Dixon, L., Leach, S., Small, R., Hite, R.D., Haponik, E. (2008) 'Early intensive care unit mobility therapy in the treatment of acute respiratory failure.' *Crit Care Med,* 36(8) pp. 2238–43.

Morris, P., Berry, M.J., Files, J.D., Thompson, J.C., Hauser, J., Flores, L., Dhar, S., Chmelo, E., Lovato, J., Case, L.D., Bakhru, R.N., Sarwal, A., Parry, S.M.,

Campbell, P., Mote, A., Winkelman, C., Hit, R.D., Nicklas, B., Chatterjee, A., Young, M.P. (2016) 'Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure.' ' *JAMA* 315:pp 2694-2702.

Needham, D.M., Davidson, J., Cohen, H., Hopkins, R.O., Weinert, C., Wunsch, H., Zawistowski, C., Bemis-Dougherty, A., Berney, S.C., Bienvenu, O.J., Brady, S.L., Brodsky, M.B., Denehy, L., Elliott, D., Flatley, C., Harabin, A.L., Jones, C., Louis, D., Meltzer, W., Muldoon, S.R., Palmer, J.B., Perme, C., Robinson, M., Schmidt, D.M., Scruth, E., Spill, G.R., Storey, C.P., Render, M., Votto, J., Harvey, M.A. (2012) 'Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference.' *Crit Care Med,* 40(2) pp. 502–9.

Needham, D., Korupolu, R., Zanni, J., Pradhan, P., Colantuoni, E., Palmer, J.B., Brower, R.G., Fan, E. (2010) 'Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project.' *Arch Phys Med Rehabil,* 91(4) pp. 536–42.

National health service [NHS] England. (2016) Improving outcomes through personalised medicine. Leeds: NHS England. [online] Accessed 20th December 2017] https://www.england.nhs.uk/wp-content/uploads/2016/09/improving-outcomes-personalised-medicine.pdf

National Institute for Health and Care Excellence [NICE]. (2007) *Acutely ill patients in hospital: Recognition of and response to acute illness in adults in hospital.* London: NICE (NICE guideline no 50).

National Institute for Health and Care Excellence [NICE]. (2009) *Rehabilitation after critical illness.* London: NICE (Nice guideline no 83)

National Institute for Health and Care Excellence [NICE]. (2017) *Rehabilitation after critical illness.* London: NICE (Nice quality standard no 158)

Parker, A., Tehranchi, K.M., Needham, D.M. (2013) 'Critical care rehabilitation trials: the importance of 'usual care'.' *Crit Care,* 17(5)183. [online] [Accessed on 20th September 2017] DOI: 10.1186/cc12884.

Parry, S.M., Remedios, L., Denehy, L., Knight, L.D., Rollinson, T.C., Berney, S., Puthucheary, Z.A., Morris, P., Granger, C.L. (2016) 'What factors affect implementation of early rehabilitation into intensive care unit practice? A qualitative study with clinicians.' *Journal of critical Care*, 12(38) pp. 137-143.

Pronovost, P., Berenholtz, S., Needham, D. (2008) 'Translating evidence into practice: a model for large scale knowledge translation.' *BMJ,* 337, October, pp. 965-965.

Puthacheary, Z., Rawal, J.,McPhail, M., Connolly,B., Ratnayake, G., Chan,P., Hopkinson, N., Padhke, R., Dew, T., Sidhu, P.S., Velloso, C., Seymour, J., Agley, C.C., Selby, A., Limb, M., Edwards, L.M., Smith, K., Rowlerson, A., Rennie, M.J., Moxham, J., Harridge, S.D., Hart, N., Montgomery, H.E. (2013) 'Acute skeletal muscle wasting in critical illness.' *JAMA*, 310(15) pp. 1591-600.

Reed, J.E., Card, A.J. (2016) 'The problem with Plan-Do-Study-Act cycles.' *BMJ Quality and Safety.* 25, pp. 147-152.

Schweickert, W., Pohlman, M.C., Pohlman, A.S., Nigos, C., Pawlik, A.J., Esbrook, C.L., Spears, L., Miller, M., Franczyk, M., Deprizio, D., Schmidt, G.A., Bowman, A., Barr, R., McCallister, K.E., Hall, J.B., Kress, J.P. (2009) 'Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial.' *Lancet*, 373(9678) pp. 1874–82.

Snelson, C., Jones, C., Atkins, G., Hodson, J., Whitehouse, T., Veenith, T., Thickett, D., Reeves, E., McLaughlin, A., Cooper, L., McWilliams, D. (2017) 'A comparison of earlier and enhanced rehabilitation of mechanically ventilated patients in critical care compared to standard care (REHAB): study protocol for a single-site randomised controlled feasibility trial.' *Pilot and Feasibility Studies*, 17(3):19 [online] [Accessed 20th September 2017] DOI: 10.1186/s40814-017-0131-1.

Stone, M.E. Jr., Snetman, D., O'Neill, A., Cucuzzo, J., Lindner, J., Ahmad, S., Teperman, S. (2011) 'Daily multidisciplinary rounds to implement the ventilator bundle decreases ventilator-associated pneumonia in trauma patients: but does it affect outcome?' *Surg Infect*, 12(5) pp. 373-8.

Taito, S., Shime, N., Ota, K., Yasuda, H. (2016) 'Early mobilization of mechanically ventilated patients in the intensive care unit.' *J Intensive Care*, 4(5) pp. 1–7.

Thomsen, G.E., Snow, G.L., Rodriguez, L., Hopkins, R.O. (2008) 'Patients with respiratory failure increase ambulation after transfer to an intensive care unit where early activity is a priority.' *Crit Care Med,* 36(4) pp. 1119-1124.

U.S. Department of Health and Human Services Health Resources and Services Administration (2011) Quality Improvement. [online] Accessed: 1st September 2017 Available from hrsa.gov/ quality/toolbox/508pdfs/qualityimprovement.pd

Volpi, E., Kobayashi, H., Shefflied-Moore, M., Mittendorfer, B.,Wolfe, R.R. (2014) 'Essential amino acids are primarily responsible for the amino acid stimulation of muscle protein anabolism in healthy elderly adults.' *Am J Clin Nutr,* 78(2)pp.250-8

Wang, Y.T., Haines, T.P., Ritchie, P., Walker, C., Ansell, T.A., Ryan, D.T., Lim, P.S., Vij, S., Acs, R., Fealy, N., Skinner, E.H. (2014) 'Early mobilization on continuous renal replacement therapy is safe and may improve filter life.' *Crit Care*, 18(4):R161 [online] {Accessed on 20th September 2017] DOI: 10.1186/cc14001.

Weber, K.T., Janicki, J.S., (1985) Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. *American Journal of Cardiology*. **55**, pp22A-31A.

Wright, S.E., Thomas, K., Watson, G., 3 Baker, C., Bryant, A., Chadwick, T.J., Shen, J., Wood, R., Wilkinson, J., Mansfield, L., Stafford, V., Wade, C., Furneval, J., Henderson, A., Hugill, K., Howard, P., Roy, A., Bonner, S., Baudouin, S. (2017) 'Intensive versus standard physical rehabilitation therapy in the critically ill

(EPICC): a multicentre, parallel-group, randomised controlled trial.' *Thorax*. [online] 'Epub ahead of print' published 5th August 2017 [Accessed on 20th September 2017] DOI: 10.1136/thoraxjnl-2016-209858

Appendix 1 – Additional peer reviewed publications and book chapters not included as part of this thesis

McWilliams, D. (2017) 'Implementation of early and structured rehabilitation in ICU: The importance of multidisciplinary team working and communication.' *Intensive Care Unit Management & Practice*, 17(4) pp. 250-252

McWilliams, D.J. (2017) 'Reading between the lines, the key to successfully implementing early rehabilitation in critical care.' *Intensive and Critical care Nursing*. 42, October pp. 5-7

Weblin, J., **McWilliams, D.,** Tucker, O. (2017) 'Feasibility of implementing prehabilitation in patients undergoing major oesophagogastric cancer resection: a single centre experience.' *Association of Chartered Physiotherapists in Respiratory Care Journal.* 49, January pp. 82-94

McWilliams, D.J., Atkins, G., Hodson, J., Boyers, M., Lea, T., Snelson, C. (2016) 'Feasibility and reliability of the Manchester Mobility Score as a measure of physical function within the Intensive Care Unit.' *Association of Chartered Physiotherapists in Respiratory Care Journal.* 48, January, pp. 26-33.

McWilliams, D.J., Duffy, L., Snelson, C. (2016) 'Current rehabilitation practices for patients admitted to critical care in the UK: a 5 day point prevalence survey of 12 adult general intensive care units.' *Association of Chartered Physiotherapists in Respiratory Care Journal.* 48, January, pp. 5-13

Edwards, J., **McWilliams, D.**, Thomas, M., Shah, S. (2014) 'Electrical muscle stimulation in the intensive care unit: an integrative review.' *Journal of the Intensive Care Society.* 15(2) pp. 142-149.

McWilliams, D.J., Westlake, E.V., Griffiths, R.D. (2011) 'Weakness on the Intensive Care Unit – Current Therapies.' *British Journal of Intensive care*. Summer edition. pp. 23-27

McWilliams, D.J., Pantelides, K.P. (2008) 'Does Physiotherapy led early mobilisation affect length of stay on ICU.' *Association of Chartered Physiotherapists in Respiratory Care Journal.* 40 pp. 5-11

Book Chapters

McWilliams D.J., Hough, A. (2017) 'Critical care, support and monitoring.' *In*: Hough A. (ed.) *Hough's Cardiorespiratory Care.* 5th ed., Elsevier, pp. 431 – 476.

McWilliams, D.J., Hough, A. (2017) ‘Physiotherapy for critically ill patients.’ *In*: Hough A. (ed.) *Hough's Cardiorespiratory Care.* 5th ed., Elsevier, pp. 477 – 518.

McWilliams, D.J., Lea, T., Hough, A. (2017) ‘Modifications for different disorders.’ *In*: Hough A. (ed.) *Hough's Cardiorespiratory Care.* 5th ed., Elsevier, pp. 519 – 554.

McWilliams, D.J., Thomas, A. (2013) .Chapter 16 Physical Mobility and Exercise Interventions for Critically Ill Patients.. *In*: Mallet, J., Albarran, J.W., Richardson, A. (eds.) *Critical Care Manual of Clinical Procedures and Competencies*. Wiley, Oxford

Appendix 2 –

Publications included in this thesis